(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 September 2003 (25.09.2003)

PCT

(10) International Publication Number
WO 03/077857 A2

(51) International Patent Classification[7]: A61K

(21) International Application Number: PCT/US03/07671

(22) International Filing Date: 12 March 2003 (12.03.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/364,929 15 March 2002 (15.03.2002) US

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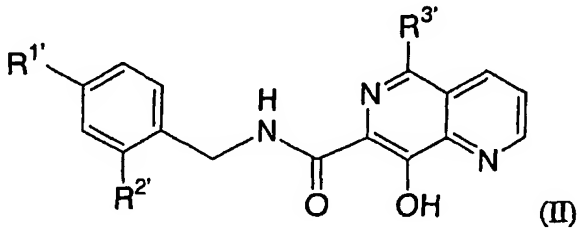
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: N-(SUBSTITUTED BENZYL)-8-HYDROXY-1,6-NAPHTHYRIDINE-7- CARBOXAMIDES USEFUL AS HIV INTEGRASE INHIBITORS



(II)

(57) Abstract: N-(Substituted benzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamides are inhibitors of HIV integrase and inhibitors of HIV replication. In one embodiment, the naphthyridine carboxamides are of Formula (II): (II),wherein R1', R2' and R3' are defined herein. The compounds are useful in the prevention and treatment of infection by HIV and in the prevention, delay in the onset, and treatment of AIDS. The compounds are employed against HIV infection and AIDS as compounds per se or in the form of pharmaceutically acceptable salts. The compounds and their salts can be employed as ingredients in pharmaceutical compositions, optionally in combination with other antivirals, immunomodulators, antibiotics or vaccines. Methods of preventing, treating or delaying the onset of AIDS and methods of preventing or treating infection by HIV are described.

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N-(SUBSTITUTED BENZYL)-8-HYDROXY-1,6-NAPHTHYRIDINE-7-CARBOXAMIDES USEFUL AS HIV INTEGRASE INHIBITORS

This application claims the benefit of U.S. Provisional Application No. 60/364,929, filed March 15, 2002, the disclosure of which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention is directed to N-(substituted benzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamides and pharmaceutically acceptable salts thereof, their synthesis, and their use as inhibitors of the HIV integrase enzyme. The compounds of the present invention and their pharmaceutically acceptable salts are useful for preventing or treating infection by HIV and for treating, delaying the onset of, or preventing AIDS.

BACKGROUND OF THE INVENTION

A retrovirus designated human immunodeficiency virus (HIV) is the etiological agent of the complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome; AIDS) and degeneration of the central and peripheral nervous system. This virus was previously known as LAV, HTLV-III, or ARV. A common feature of retrovirus replication is the insertion by virally-encoded integrase of proviral DNA into the host cell genome, a required step in HIV replication in human T-lymphoid and monocytoid cells. Integration is believed to be mediated by integrase in three steps: assembly of a stable nucleoprotein complex with viral DNA sequences; cleavage of two nucleotides from the 3' termini of the linear proviral DNA; covalent joining of the recessed 3' OH termini of the proviral DNA at a staggered cut made at the host target site. The fourth step in the process, repair synthesis of the resultant gap, may be accomplished by cellular enzymes.

Nucleotide sequencing of HIV shows the presence of a pol gene in one open reading frame [Ratner et al., *Nature* 1985, 313: 277]. Amino acid sequence homology provides evidence that the pol sequence encodes reverse transcriptase, integrase and an HIV protease [Toh et al., *EMBO J.* 1985, 4: 1267;

Power et al., *Science* 1986, 231: 1567; Pearl et al., *Nature* 1987, 329: 351]. All three enzymes have been shown to be essential for the replication of HIV.

It is known that some antiviral compounds which act as inhibitors of HIV replication are effective agents in the treatment of AIDS and similar diseases, including reverse transcriptase inhibitors such as azidothymidine (AZT) and efavirenz and protease inhbitors such as indinavir and nelfinavir. The compounds of this invention are inhibitors of HIV integrase and inhibitors of HIV replication. The inhibition of integrase in vitro and of HIV replication in cells is a direct result of inhibiting the strand transfer reaction catalyzed by the recombinant integrase in vitro in HIV infected cells. A particular advantage of the present invention is highly specific inhibition of HIV integrase and HIV replication.

The following references are of interest as background:

Chemical Abstracts No. 33-2525 discloses the preparation of 5-chloro-8-hydroxy-1,6-naphthyridine-7-carboxylic acid amide from the corresponding methyl ester.

US 5,294,620 discloses certain 1,6-naphthyridin-2-one derivatives having angiotensin II antagonist activity.

US _____ (Publication of U.S. Application Serial No. 09/973,853, filed October 10, 2001) and WO 02/30930 (Publication of International Application No. PCT/US 01/31456, filed October 9, 2001) each disclose certain 8-hydroxy-1,6-naphthyridine-7-carboxamides which are HIV integrase inhibitors useful, *inter alia*, for treating HIV infection and AIDS.

SUMMARY OF THE INVENTION

The present invention is directed to certain N-(substituted benzyl)-8-hydroxy- 1,6-naphthyridine-7-carboxamides. These compounds are useful in the inhibition of HIV integrase, the prevention of infection by HIV, the treatment of infection by HIV and in the prevention, treatment, and delay in the onset of AIDS and/or ARC, either as compounds or their pharmaceutically acceptable salts, or as pharmaceutical composition ingredients, whether or not in combination with other HIV/AIDS antivirals, anti-infectives, immunomodulators, antibiotics or vaccines. The compounds of the invention have one or more polar ortho substituents in the benzyl ring. The compounds can have improved potency against replication of HIV in cells relative to similar N-(benzyl)-8-hydroxy-1,6-napthyridine carboxamides

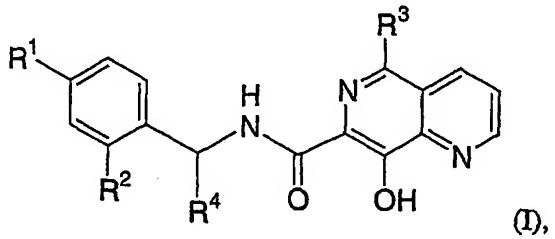
which either have no ortho substituents on the benzyl ring or have non-polar or less polar ortho substituents.

Various embodiments, aspects and features of the present invention are either further described in or will be apparent from the ensuing description, examples and appended claims.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to certain N-(substituted benzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide compounds. These compounds and pharmaceutically acceptable salts thereof are HIV integrase inhibitors. The compounds of the present invention are characterized by having at least one ortho polar substituent (e.g., -C(=O)N(alkyl)$_2$, -C(=O)NH(alkyl), -alkylene-C(=O)N(alkyl)$_2$, or -alkylene-C(=O)NH(alkyl)) on the benzyl ring. The compounds of the invention can have improved cell potency (i.e., antiviral potency as determined, for example, via an assay to measure inhibition of HIV replication), particularly in the presence of human serum, relative to similar N-benzyl-8-hydroxy-1,6-naphthyridine carboxamide HIV integrase inhibitors that do not have an ortho polar substituent or have non-polar or less polar ortho substituents.

A first embodiment of the present invention is a compound of Formula (I):



(I),

wherein R1 is -H or halogen;

R2 is:

(1) -C$_{1-6}$ alkyl, optionally substituted with from 1 to 3 substituents each of which is independently -OH, -O-C$_{1-6}$ alkyl, -O-C$_{1-6}$ haloalkyl, -CN, -NO$_2$, -N(R^{a}R^b), -C(=O)N(R^{a}R^b), -C(=O)R^a, -CO$_2$R^c, -OCO$_2$R^c, -S(O)$_n$R^c, -SO$_2$N(R^{a}R^b), -N(R^a)C(=O)R^b, -N(R^a)CO$_2$R^c,

$-N(R^a)SO_2R^c$, $-N(R^a)SO_2N(R^aR^b)$, $-OC(=O)N(R^aR^b)$, or $-N(R^a)C(=O)N(R^aR^b)$,

(2) $-O-C_{1-6}$ alkyl, optionally substituted with from 1 to 3 substituents each of which is independently -OH, $-O-C_{1-6}$ alkyl, $-O-C_{1-6}$ haloalkyl, $-S(O)_nR^c$, $-N(R^a)-CO_2R^c$, $-C(=O)N(R^aR^b)$, $-SO_2N(R^aR^b)$, $-N(R^a)C(=O)R^b$, $-N(R^a)CO_2R^c$, $-N(R^a)SO_2R^c$, $-N(R^a)SO_2N(R^aR^b)$, $-OC(=O)N(R^aR^b)$, or $-N(R^a)C(=O)N(R^aR^b)$,

(3) $-C_{1-6}$ haloalkyl,

(4) $-O-C_{1-6}$ haloalkyl,

(5) -OH,

(6) halo,

(7) $-NO_2$,

(8) -CN,

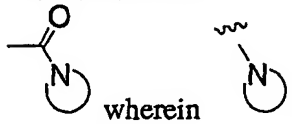
(9) $-C(=O)R^a$,

(10) $-CO_2R^c$,

(11) $-SO_2N(R^aR^b)$,

(12) $-N(R^aR^b)$,

(13) $-C(=O)N(R^aR^b)$,

(14)  wherein is azetidinyl, pyrrolidinyl, piperidinyl, or morpholino,

(15) $-N(R^a)SO_2R^c$,

(16) $-OC(=O)N(R^aR^b)$,

(17) $-N(R^a)C(=O)N(R^aR^b)$,

(18) $-N(R^a)-C_{1-6}$ alkyl-$C(=O)N(R^aR^b)$,

(19) $-N(R^a)-C(=O)-C_{1-6}$ alkyl-$N(R^aR^b)$,

(20) $-N(R^a)C(=O)-C(=O)N(R^aR^b)$,

(21) $-OCO_2R^c$,

(22) $-N(R^a)-SO_2N(R^aR^b)$,

(23) $-N(R^a)-SO_2-C_{1-6}$ alkyl-$N(R^aR^b)$,

(24) $-N(R^a)C(=O)R^b$,

(25) $-N(R^a)CO_2R^c$,

(26) $-S-C_{1-6}$ alkyl-$C(=O)N(R^aR^b)$,

(27) -N(SO_2R^c)-C_{1-6} alkyl-C(=O)N(R^aR^b),
(28) -N(R^a)-C(=O)-C_{1-6} alkyl-C(=O)N(R^aR^b),
(29) -N(R^a)-C(=O)-C_{1-6} alkyl-N(R^a)C(=O)(R^b),
(30) -N(R^a)-SO_2-C_{1-6} alkyl-C(=O)N(R^aR^b),
(31) -N(R^a)-SO_2-C_{1-6} alkyl-N(R^a)C(=O)(R^b),
(32) -C(=O)N(R^a) -C_{1-6} alkyl-C(=O)N(R^aR^b),
(33) -C(=O)N(R^a)-C_{1-6} alkyl-N(R^a)C(=O)(R^b), with the proviso that the -N(Ra)- moieties are not both attached to the same carbon atom of the -C_{1-6} alkyl- moiety,
(34) -C(=O)N(R^a)-C_{1-6} alkyl-O-C_{1-3} alkyl, with the proviso that the -N(Ra)- moiety and the -O-C_{1-3} alkyl group are not both attached to the same carbon atom of the -C_{1-6} alkyl- moiety,
(35) -C(=O)N(R^a)-C_{1-6} alkyl-$S(O)_nR^c$,
(36) -HetA,
(37) -HetB,
(38) -C_{1-6} alkyl-HetA, or
(39) -C_{1-6} alkyl-HetB;

HetA is a 5- or 6-membered heteraromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S; and wherein the heteroaromatic ring is optionally substituted with from 1 to 3 substituents each of which is independently halogen, -OH, -C_{1-6} alkyl, -C_{3-6} cycloalkyl, -C_{1-6} alkyl-O-C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, -N(R^aR^b), -C_{1-6} alkyl-N(R^aR^b), -C(=O)N(R^aR^b), -C_{1-6} alkyl-C(=O)N(R^aR^b), -C(=O)R^a, -C_{1-6} alkyl-C(=O)R^a, -CO_2R^c, -C_{1-6} alkyl-CO_2R^c, -OCO_2R^c, -C_{1-6} alkyl-OCO_2R^c, -$S(O)_nR^c$, -C_{1-6} alkyl-$S(O)_nR^c$, -$SO_2N(R^aR^b)$, -C_{1-6} alkyl-$SO_2N(R^aR^b)$, -N(R^a)SO_2R^c, -C_{1-6} alkyl-N(R^a)SO_2R^c, -N(R^a)C(=O)R^b, -C_{1-6} alkyl-N(R^a)C(=O)R^b, -N(R^a)CO_2R^c, -C_{1-6} alkyl-N(R^a)CO_2R^c, phenyl, -C_{1-6} alkyl-phenyl, or oxo;

HetB is a 4- to 7-membered saturated or mono-unsaturated heterocyclic ring containing 1 to 4 heteroatoms independently selected from N, O and S; and wherein the saturated heterocyclic ring is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -OH, -C_{1-6} alkyl, -C_{3-6} cycloalkyl, -C_{1-6} alkyl-O-C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, -N(R^aR^b),

-C_{1-6} alkyl-$N(R^aR^b)$, $-C(=O)N(R^aR^b)$, -C_{1-6} alkyl-$C(=O)N(R^aR^b)$, $-C(=O)R^a$, -C_{1-6} alkyl-$C(=O)R^a$, $-CO_2R^c$, -C_{1-6} alkyl-CO_2R^c, $-OCO_2R^c$, -C_{1-6} alkyl-OCO_2R^c, $-S(O)_nR^c$, -C_{1-6} alkyl-$S(O)_nR^c$, $-SO_2N(R^aR^b)$, -C_{1-6} alkyl-$SO_2N(R^aR^b)$, $-N(R^a)SO_2R^c$, -C_{1-6} alkyl-$N(R^a)SO_2R^c$, $-N(R^a)C(=O)R^b$, -C_{1-6} alkyl-$N(R^a)C(=O)R^b$, $-N(R^a)CO_2R^c$, -C_{1-6} alkyl-$N(R^a)CO_2R^c$, phenyl, -C_{1-6} alkyl-phenyl, or oxo;

R^3 is

(1) -H,

(2) $-C(=O)N(R^aR^b)$,

(3) -C_{1-6} alkyl-$C(=O)N(R^aR^b)$,

(4) -S-C_{1-6} alkyl-$C(=O)N(R^aR^b)$,

(5) -O-C_{1-6} alkyl-$C(=O)N(R^aR^b)$,

(6) $-N(R^a)-C(R^b)=O$,

(7) $-N(SO_2R^c)$-C_{1-6} alkyl-$C(=O)N(R^aR^b)$,

(8) $-N(R^a)-C(=O)-C(=O)-N(R^aR^b)$,

(9) $-N(R^a)SO_2R^c$,

(10) $-SO_2N(R^aR^b)$,

(11) $-CH=CH-C(=O)-N(R^aR^b)$,

(12) $-N(R^a)$-C_{1-6} alkyl-$C(=O)N(R^aR^b)$,

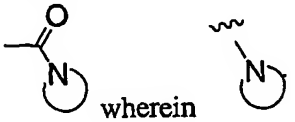
(13) $-N(R^a)-C(=O)-N(R^aR^b)$,

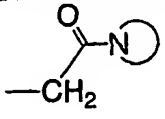
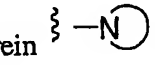
(14) -HetC,

(15) -C_{1-6} alkyl-HetC,

(16) $-N(R^a)$-C_{1-6} alkyl-HetC,

(17) -HetQ,

(18)  wherein is as defined above in R^2 (i.e., azetidinyl, pyrrolidinyl, piperidinyl, or morpholinyl), or

(19)  wherein  is as defined above in R^2;

HetC is a 4- to 7-membered saturated heterocyclic ring containing from 1 to 4 heteratoms independently selected from N, O and S, wherein the saturated

heterocyclic ring is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-4} alkyl, -C_{3-6} cycloalkyl, -O-C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} haloalkyl, -CN, oxo, phenyl, benzyl, phenylethyl, -$(CH_2)_{0-3}C(=O)N(R^aR^b)$, -$(CH_2)_{0-3}C(=O)R^a$, -$N(R^a)$-$C(=O)R^b$, -$N(R^a)$-$CO_2R^c$, -$(CH_2)_{1-3}N(R^a)$-$C(=O)R^b$, -$N(R^aR^b)$, -$(CH_2)_{1-3}N(R^aR^b)$, -$SO_2R^c$, -$(CH_2)_{0-3}C(=O)$-HetD, -HetD, -$N(R^a)$-HetD, and -$(CH_2)_{1-3}$-HetD; wherein each HetD is independently a 5- or 6-membered heteroaromatic ring containing from 1 to 4 nitrogen atoms or a 5- or 6-membered saturated heterocyclic ring containing from 1 to 4 nitrogen atoms, wherein the ring is optionally substituted with 1 or 2 substituents each of which is independently halogen, oxo, -C_{1-4} alkyl, or -O-C_{1-4} alkyl;

HetQ is a 7- to 9-membered bridged azabicycloalkyl saturated ring system containing a C_{5-7} azacycloalkyl ring in which two of the ring carbons are connected by a bridge containing 1 or 2 carbon atoms; wherein the bridged azabicycloalkyl ring system is optionally substituted with from 1 to 4 substituents each of which is independently halogen, oxo, or -C_{1-4} alkyl;

R^4 is -H or -$C(=O)N(R^aR^b)$;

each R^a is independently -H, -C_{1-6} alkyl, -C_{1-6} haloalkyl, or -C_{3-6} cycloalkyl;

each R^b is independently -H, -C_{1-6} alkyl, -C_{1-6} haloalkyl, or -C_{3-6} cycloalkyl;

each R^c is independently -C_{1-6} alkyl, -C_{1-6} haloalkyl, or -C_{3-6} cycloalkyl; and

each n is independently an integer equal to zero, 1, or 2;

or a pharmaceutically acceptable salt thereof.

A first aspect of the first embodiment of the present invention is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^3 is restricted to one of groups (1) to (16); and all other variables are as defined in the first embodiment.

A second aspect of the first embodiment is a compound of Formula (I), wherein R^1 is -H or -F; and all other variables are as originally defined above; or a pharmaceutically acceptable salt thereof.

A third aspect of the first embodiment is a compound of Formula (I), wherein R^1 is -H or -F; and all other variables are as defined in the first aspect of the first embodiment; or a pharmaceutically acceptable salt thereof.

A fourth aspect of the first embodiment is a compound of Formula (I), wherein R^1 is -F; and all other variables are as originally defined above; or a pharmaceutically acceptable salt thereof.

A fifth aspect of the first embodiment is a compound of Formula (I), wherein R^1 is -F; and all other variables are as defined in the first aspect of the first embodiment; or a pharmaceutically acceptable salt thereof.

A sixth aspect of the first embodiment is a compound of Formula (I), wherein R^2 is:

(1) -C_{1-6} alkyl substituted with one of -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, -C(=O)N(R^aR^b), -S(O)$_n$$R^c$, -$SO_2$N($R^aR^b$), -N($R^a$)C(=O)$R^b$, -N($R^a$)$CO_2R^c$, -N($R^a$)$SO_2R^c$, -N($R^a$)$SO_2$N($R^aR^b$), -OC(=O)N($R^aR^b$), or -N($R^a$)C(=O)N($R^aR^b$),

(2) -O-C_{1-6} alkyl, optionally substituted with one of -OH, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, -S(O)$_n$$R^c$, -N($R^a$)-$CO_2R^c$, -C(=O)N($R^aR^b$), -$SO_2$N($R^aR^b$), -N($R^a$)C(=O)$R^b$, -N($R^a$)$CO_2R^c$, -N($R^a$)$SO_2R^c$, -N($R^a$)$SO_2$N($R^aR^b$), -OC(=O)N($R^aR^b$), or -N($R^a$)C(=O)N($R^aR^b$),

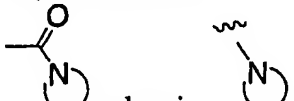
(3) -O-C_{1-6} haloalkyl,

(4) halo,

(5) -SO_2N(R^aR^b),

(6) -N(R^aR^b),

(7) -C(=O)N(R^aR^b),

(8)  wherein is azetidinyl, pyrrolidinyl, piperidinyl, or morpholino,

(9) -N(R^a)SO_2R^c,

(10) -OC(=O)N(R^aR^b),

(11) -N(R^a)C(=O)N(R^aR^b),

(12) -N(R^a)-C_{1-6} alkyl-C(=O)N(R^aR^b),

(13) $-N(R^a)-C(=O)-C_{1-6}$ alkyl-$N(R^aR^b)$,
(14) $-N(R^a)C(=O)-C(=O)N(R^aR^b)$,
(15) $-OCO_2R^c$,
(16) $-N(R^a)-SO_2N(R^aR^b)$,
(17) $-N(R^a)-SO_2-C_{1-6}$ alkyl-$N(R^aR^b)$,
(18) $-N(R^a)C(=O)R^b$,
(19) $-N(R^a)CO_2R^c$,
(20) $-S-C_{1-6}$ alkyl-$C(=O)N(R^aR^b)$,
(21) $-N(SO_2R^c)-C_{1-6}$ alkyl-$C(=O)N(R^aR^b)$,
(22) $-N(R^a)-C(=O)-C_{1-6}$ alkyl-$C(=O)N(R^aR^b)$,
(23) $-N(R^a)-C(=O)-C_{1-6}$ alkyl-$N(R^a)C(=O)(R^b)$,
(24) $-N(R^a)-SO_2-C_{1-6}$ alkyl-$C(=O)N(R^aR^b)$,
(25) $-N(R^a)-SO_2-C_{1-6}$ alkyl-$N(R^a)C(=O)(R^b)$,
(26) $-C(=O)N(R^a)$ $-C_{1-6}$ alkyl-$C(=O)N(R^aR^b)$,
(27) $-C(=O)N(R^a)-C_{1-6}$ alkyl-$N(R^a)C(=O)(R^b)$, with the proviso that the -N(Ra)- moieties are not both attached to the same carbon atom of the $-C_{1-6}$ alkyl- moiety,
(28) $-C(=O)N(R^a)-C_{1-6}$ alkyl-$O-C_{1-3}$ alkyl, with the proviso that the -N(Ra)- moiety and the $-O-C_{1-3}$ alkyl group are not both attached to the same carbon atom of the $-C_{1-6}$ alkyl- moiety,
(29) $-C(=O)N(R^a)-C_{1-6}$ alkyl-$S(O)_nR^c$,
(30) -HetA,
(31) -HetB,
(32) $-C_{1-6}$ alkyl-HetA, or
(33) $-C_{1-6}$ alkyl-HetB;

and all other variables are as originally defined in the first embodiment;

or a pharmaceutically acceptable salt thereof.

A seventh aspect of the first embodiment is a compound of Formula (I), wherein R^2 is as defined in the sixth aspect; and all other variables are as defined in the first aspect; or a pharmaceutically acceptable salt thereof.

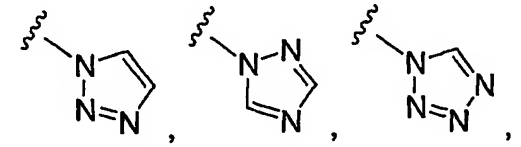
A feature of either the sixth or the seventh aspect is a compound of Formula (I), wherein R^2 is as defined in the sixth or seventh aspect, except that HetA in the definition of R^2 is a 5- or 6-membered heteraromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S; and wherein the heteroaromatic ring is optionally substituted with from 1 to 3 substituents each of which is independently -C_{1-6} alkyl, -C_{3-6} cycloalkyl, -C(=O)N(R^aR^b), -C_{1-6} alkyl-C(=O)N(R^aR^b), -$S(O)_nR^c$, -C_{1-6} alkyl-$S(O)_nR^c$, -$SO_2N(R^aR^b)$, -C_{1-6} alkyl-$SO_2N(R^aR^b)$, -$N(R^a)SO_2R^c$, -C_{1-6} alkyl-$N(R^a)SO_2R^c$, -$N(R^a)C(=O)R^b$, -C_{1-6} alkyl-$N(R^a)C(=O)R^b$, or oxo; and

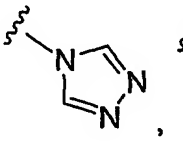
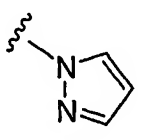
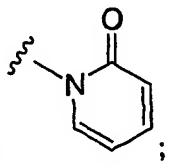
HetB in the definition of R^2 is a 4- to 7-membered saturated or mono-unsaturated heterocyclic ring containing 1 to 4 heteroatoms independently selected from N, O and S; and wherein the saturated heterocyclic ring is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl, -C_{3-6} cycloalkyl, -C(=O)N(R^aR^b), -C_{1-6} alkyl-C(=O)N(R^aR^b), -$S(O)_nR^c$, -C_{1-6} alkyl-$S(O)_nR^c$, -$SO_2N(R^aR^b)$, -C_{1-6} alkyl-$SO_2N(R^aR^b)$, -$N(R^a)SO_2R^c$, -C_{1-6} alkyl-$N(R^a)SO_2R^c$, -$N(R^a)C(=O)R^b$, -C_{1-6} alkyl-$N(R^a)C(=O)R^b$, or oxo;

and all other variables are as originally defined in the first embodiment or as defined in the first aspect thereof;

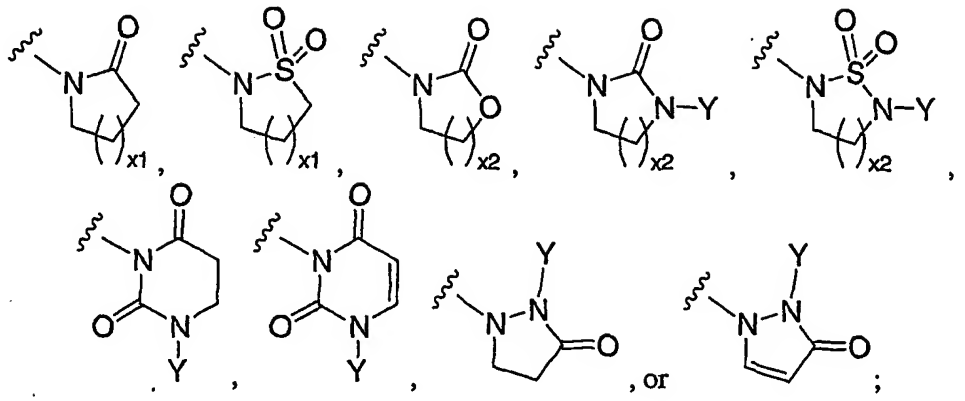
or a pharmaceutically acceptable salt thereof.

Another feature of either the sixth or the seventh aspect of the first embodiment is a compound of Formula (I), wherein R^2 is as defined in the sixth or seventh aspect, except that HetA in the definition of R^2 is:



HetB is:



Y is -H, -C_{1-6} alkyl, -C_{3-6} cycloalkyl, or -C_{1-6} haloalkyl;

x1 is an integer equal to zero, 1 or 2; and

x2 is an integer equal to 1, 2, or 3;

and all other variables are as originally defined in the first embodiment or as defined in the first aspect thereof;

or a pharmaceutically acceptable salt thereof.

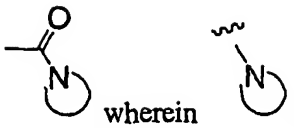
An eighth aspect of the first embodiment is a compound of Formula (I), wherein R^2 is:

(1) -C_{1-6} alkyl substituted with one of -O-C_{1-6} haloalkyl, -C(=O)N(R^aR^b), -S(O)$_n$$R^c$, -$SO_2$N($R^aR^b$), -N($R^a$)C(=O)$R^b$, -N($R^a$)$CO_2R^c$, -N($R^a$)$SO_2R^c$, -N($R^a$)$SO_2$N($R^aR^b$), -OC(=O)N($R^aR^b$), or -N($R^a$)C(=O)N($R^aR^b$),

(2) -O-C_{1-6} alkyl substituted with one of -OH, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, -S(O)$_n$$R^c$, or -N($R^a$)-$CO_2R^c$, -C(=O)N($R^aR^b$), -$SO_2$N($R^aR^b$), -N($R^a$)C(=O)$R^b$, -N($R^a$)$CO_2R^c$, -N($R^a$)$SO_2R^c$, -N($R^a$)$SO_2$N($R^aR^b$), -OC(=O)N($R^aR^b$), or -N($R^a$)C(=O)N($R^aR^b$),

(3) -SO_2N(R^aR^b),

(4) -C(=O)N(R^aR^b),

(5)  wherein is azetidinyl, pyrrolidinyl, piperidinyl, or morpholino,

(6) $-N(R^a)SO_2R^c$,

(7) $-OC(=O)N(R^aR^b)$,

(8) $-N(R^a)C(=O)N(R^aR^b)$,

(9) $-N(R^a)$-C_{1-6} alkyl-$C(=O)N(R^aR^b)$,

(10) $-N(R^a)-C(=O)-C_{1-6}$ alkyl-$N(R^aR^b)$,

(11) $-N(R^a)C(=O)-C(=O)N(R^aR^b)$,

(12) $-OCO_2R^c$,

(13) $-N(R^a)-SO_2N(R^aR^b)$,

(14) $-N(R^a)-SO_2-C_{1-6}$ alkyl-$N(R^aR^b)$,

(15) $-N(R^a)C(=O)R^b$,

(16) $-N(R^a)CO_2R^c$,

(17) $-S-C_{1-6}$ alkyl-$C(=O)N(R^aR^b)$,

(18) $-N(SO_2R^c)-C_{1-6}$ alkyl-$C(=O)N(R^aR^b)$,

(19) $-N(R^a)-C(=O)-C_{1-6}$ alkyl-$C(=O)N(R^aR^b)$,

(20) $-N(R^a)-C(=O)-C_{1-6}$ alkyl-$N(R^a)C(=O)(R^b)$,

(21) $-N(R^a)-SO_2-C_{1-6}$ alkyl-$C(=O)N(R^aR^b)$,

(22) $-N(R^a)-SO_2-C_{1-6}$ alkyl-$N(R^a)C(=O)(R^b)$,

(23) $-C(=O)N(R^a)$ -C_{1-6} alkyl-$C(=O)N(R^aR^b)$,

(24) $-C(=O)N(R^a)-C_{1-6}$ alkyl-$N(R^a)C(=O)(R^b)$, with the proviso that the -N(Ra)- moieties are not both attached to the same carbon atom of the -C_{1-6} alkyl- moiety,

(25) $-C(=O)N(R^a)-C_{1-6}$ alkyl-O-C_{1-3} alkyl, with the proviso that the -N(Ra)- moiety and the -O-C_{1-3} alkyl group are not both attached to the same carbon atom of the -C_{1-6} alkyl- moiety,

(26) $-C(=O)N(R^a)-C_{1-6}$ alkyl-$S(O)_nR^c$,

(27) -HetB, or

(28) -C_{1-6} alkyl-HetB;

and all other variables are as originally defined in the first embodiment;

or a pharmaceutically acceptable salt thereof.

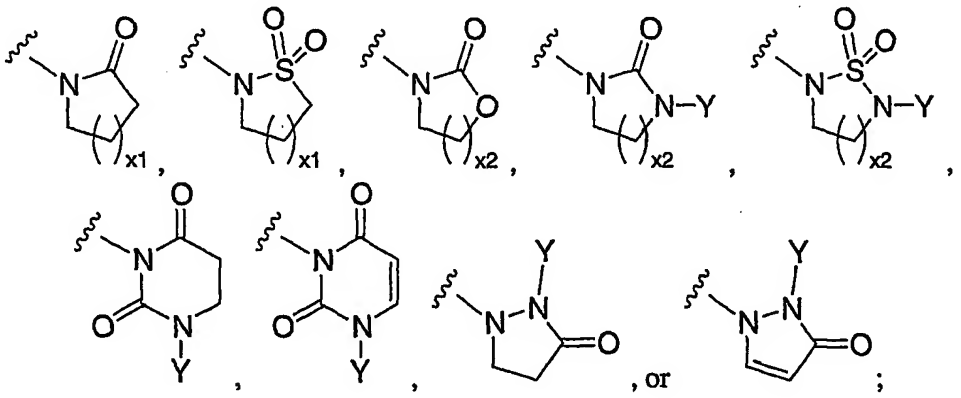
A ninth aspect of the first embodiment is a compound of Formula (I), wherein R^2 is as defined in the eighth aspect; and all other variables are as defined in the first aspect; or a pharmaceutically acceptable salt thereof.

A feature of either the eighth or the ninth aspect is a compound of Formula (I), wherein R^2 is as defined in the eighth or ninth aspect, except that HetB in the definition of R^2 is a 4- to 7-membered saturated or mono-unsaturated heterocyclic ring containing from 1 to 3 heteroatoms selected from 1 or 2 nitrogen atoms, zero or 1 oxygen atom, and zero or 1 sulfur atom; wherein the heterocyclic ring is optionally substituted with from 1 to 3 substituents each of which is independently -C_{1-6} alkyl, -C_{3-6} cycloalkyl, -C_{1-6} haloalkyl, or oxo;

and all other variables are as originally set forth in the first embodiment or as set forth in the first aspect thereof;

or a pharmaceutically acceptable salt thereof.

Another feature of either the eighth or the ninth aspect of the first embodiment is a compound of Formula (I), wherein R^2 is as defined in the eighth or the ninth aspect, except that HetB in the definition of R^2 is:



Y is -H, -C_{1-6} alkyl, -C_{3-6} cycloalkyl, or -C_{1-6} haloalkyl;

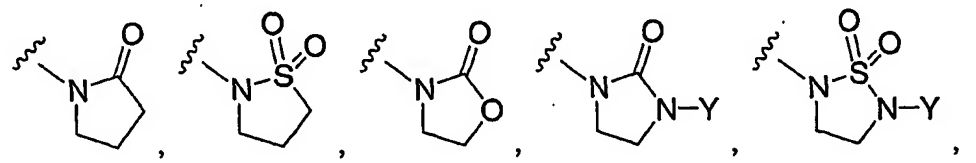
x1 is an integer equal to zero, 1 or 2; and

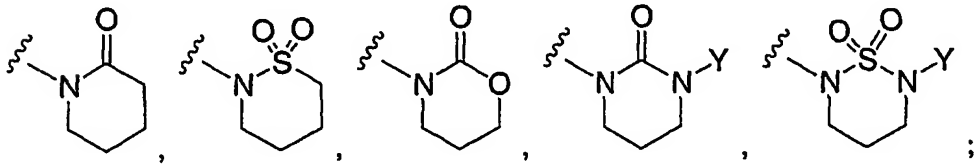
x2 is an integer equal to 1, 2, or 3;

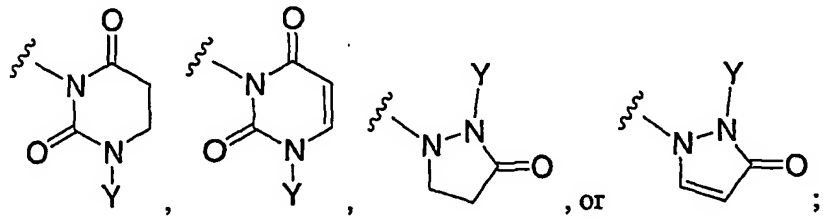
and all other variables are as originally defined in the first embodiment or as defined in the first aspect thereof;

or a pharmaceutically acceptable salt thereof.

Still another feature of either the eighth or the ninth aspect is a compound of Formula (I), wherein R^2 is as defined in the eighth or the ninth aspect, except that HetB in the definition of R^2 is:







Y is -H, methyl, ethyl, cyclopropyl, or CF_3;

and all other variables are as originally defined in the first embodiment or as defined in the first aspect thereof;

or a pharmaceutically acceptable salt thereof.

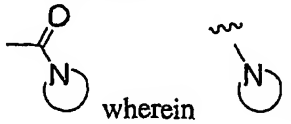
A tenth aspect of the first embodiment is a compound of Formula (I), wherein R^2 is:

(1) $-(CH_2)_{1-3}-Q$, wherein Q is $-OCF_3$, $-C(=O)N(R^aR^b)$, $-S(O)_nR^c$, $-SO_2N(R^aR^b)$, $-N(R^a)C(=O)R^b$, $-N(R^a)CO_2R^c$, $-N(R^a)SO_2R^c$, $-N(R^a)SO_2N(R^aR^b)$, $-OC(=O)N(R^aR^b)$, or $-N(R^a)C(=O)N(R^aR^b)$,

(2) $-O-(CH_2)_{1-3}-T$, wherein T is $-OH$, $-OCH_3$, $-OCF_3$, $-S(O)_nR^c$, or $-N(R^a)-CO_2R^c$,

(3) $-SO_2N(R^aR^b)$,

(4) $-C(=O)N(R^aR^b)$,

(5)  wherein is azetidinyl, pyrrolidinyl, piperidinyl, or morpholino,

(6) $-N(R^a)SO_2R^c$,

(7) $-OC(=O)N(R^aR^b)$,

(8) $-N(R^a)C(=O)N(R^aR^b)$,

(9) $-N(R^a)-(CH_2)_{1-3}-C(=O)N(R^aR^b)$,

(10) $-N(R^a)-C(=O)-(CH_2)_{1-3}-N(R^aR^b)$,

(11) $-N(R^a)C(=O)-C(=O)N(R^aR^b)$,

(12) $-OCO_2R^c$,

(13) $-N(R^a)-SO_2N(R^aR^b)$,

(14) $-N(R^a)-SO_2-(CH_2)_{1-3}-N(R^aR^b)$,

(15) $-N(R^a)C(=O)R^b$,

(16) $-N(R^a)CO_2R^c$,

(17) $-S-(CH_2)_{1-3}-C(=O)N(R^aR^b)$, or

(18) $-N(SO_2R^c)-(CH_2)_{1-3}-C(=O)N(R^aR^b)$;

(19) $-N(R^a)-C(=O)-C_{1-6}$ alkyl-$C(=O)N(R^aR^b)$,

(20) $-N(R^a)-C(=O)-C_{1-6}$ alkyl-$N(R^a)C(=O)(R^b)$,

(21) $-N(R^a)-SO_2-C_{1-6}$ alkyl-$C(=O)N(R^aR^b)$,

(22) $-N(R^a)-SO_2-C_{1-6}$ alkyl-$N(R^a)C(=O)(R^b)$,

(23) $-C(=O)N(R^a)-C_{1-6}$ alkyl-$C(=O)N(R^aR^b)$, or

(24) $-C(=O)N(R^a)-C_{1-6}$ alkyl-$N(R^a)C(=O)(R^b)$, with the proviso that the -N(Ra)- moieties are not both attached to the same carbon atom of the $-C_{1-6}$ alkyl- moiety,

(25) -C(=O)N(R^a)-C_{1-6} alkyl-O-C_{1-3} alkyl, with the proviso that the -N(Ra)- moiety and the -O-C_{1-3} alkyl group are not both attached to the same carbon atom of the -C_{1-6} alkyl- moiety,

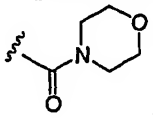
(26) -C(=O)N(R^a)-C_{1-6} alkyl-S(O)$_n$$R^c$;

and all other variables are as originally set forth in the first embodiment;

or a pharmaceutically acceptable salt thereof.

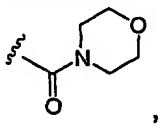
An eleventh aspect of the first embodiment is a compound of Formula (I), wherein R^2 is as defined in the tenth aspect; and all other variables are as defined in the first aspect; or a pharmaceutically acceptable salt thereof.

A twelfth aspect of the first embodiment is a compound of Formula (I),

wherein R^2 is -C_{1-6} alkyl-C(=O)N(R^aR^b), -C(=O)N(R^aR^b),  , triazolyl, or tetrazolyl;

and all other variables are as originally defined in the first embodiment;

or a pharmaceutically acceptable salt thereof.

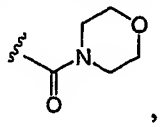
In a feature of the twelfth aspect, R^2 is -$(CH_2)_{1-3}$-C(=O)N(R^aR^b), -C(=O)N(R^aR^b),  , triazolyl, or tetrazolyl; and all other variables are as defined in the twelfth aspect; or a pharmaceutically acceptable salt thereof.

A thirteenth aspect of the first embodiment is a compound of Formula (I), wherein R^2 is -C_{1-6} alkyl-C(=O)N(R^aR^b) or -C(=O)N(R^aR^b);

and all other variables are as defined in the first aspect of the first embodiment;

or a pharmaceutically acceptable salt thereof.

In a feature of the thirteenth aspect, R^2 is $-(CH_2)_{1-3}-C(=O)N(R^aR^b)$ or $-C(=O)N(R^aR^b)$; and all other variables are as defined in the thirteenth aspect; or a pharmaceutically acceptable salt thereof.

A fourteenth aspect of the first embodiment is a compound of Formula (I), wherein R^2 is $-(CH_2)_{1-3}-C(=O)N(R^{a*}R^{b*})$, $-C(=O)N(R^{a*}R^{b*})$,  , triazolyl, or tetrazolyl;

R^{a*} and R^{b*} are each independently -H,$-C_{1-4}$ alkyl, or cyclopropyl, with the proviso that R^{a*} and R^{b*} are not both -H;

each R^a in R^3 and R^4 is independently -H, $-C_{1-4}$ alkyl, or cyclopropyl;

each R^b in R^3 and R^4 is independently -H, $-C_{1-4}$ alkyl, or cyclopropyl; and

each R^c in R^3 is independently $-C_{1-4}$ alkyl or cyclopropyl;

all all other variables are as originally set forth in the first embodiment;

or a pharmaceutically acceptable salt thereof.

In a feature of the fourteenth aspect, one of R^{a*} and R^{b*} is -H, and the other of R^{a*} and R^{b*} is $-C_{1-4}$ alkyl or cyclopropyl; and all other variables are as defined in the fourteenth aspect; or a pharmaceutically acceptable salt thereof.

A fifteenth aspect of the first embodiment is a compound of Formula (I), wherein R^2 is $-(CH_2)_{1-3}-C(=O)N(R^{a*}R^{b*})$ or $-C(=O)N(R^{a*}R^{b*})$;

R^{a*} and R^{b*} are each independently -H,$-C_{1-4}$ alkyl, or cyclopropyl, with the proviso that R^{a*} and R^{b*} are not both -H;

each R^a in R^3 and R^4 is independently -H, $-C_{1-4}$ alkyl, or cyclopropyl;

each R^b in R^3 and R^4 is independently -H, -C_{1-4} alkyl, or cyclopropyl; and

each R^c in R^3 is independently -C_{1-4} alkyl or cyclopropyl;

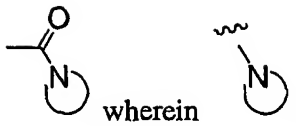
all all other variables are as set forth in the first aspect of the first embodiment;

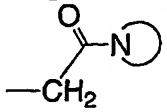
or a pharmaceutically acceptable salt thereof.

In a feature of the fifteenth aspect, one of R^{a*} and R^{b*} is -H, and the other of R^{a*} and R^{b*} is -C_{1-4} alkyl or cyclopropyl; and all other variables are as defined in the fifteenth aspect; or a pharmaceutically acceptable salt thereof.

A sixteenth aspect of the first embodiment is a compound of Formula (I), wherein R^3 is:

(1) -H,
(2) -C(=O)N(R^aR^b),
(3) -CH_2-C(=O)N(R^aR^b),
(4) -CH_2CH_2-C(=O)N(R^aR^b),
(5) -S-CH_2-C(=O)N(R^aR^b),
(6) -O-CH_2-C(=O)N(R^aR^b),
(7) -N(R^a)-C(R^b)=O,
(8) -N(SO_2R^c)-CH_2-C(=O)N(R^aR^b),
(9) -N(R^a)-C(=O)-C(=O)-N(R^aR^b),
(10) -N(R^a)SO_2R^c,
(11) -SO_2N(R^aR^b),
(12) -CH=CH-C(=O)-N(R^aR^b),
(13) -N(R^a)-CH_2-C(=O)N(R^aR^b),
(14) -N(R^a)-C(=O)-N(R^aR^b),
(15) -HetC,
(16) -(CH_2)$_{1-3}$ alkyl-HetC,
(17) -N(R^a)-(CH_2)$_{1-3}$-HetC,
(18) -HetQ,

(19)  wherein is azetidinyl, pyrrolidinyl, piperidinyl, or morpholinyl, or

(20)  wherein  is azetidinyl, pyrrolidinyl, piperidinyl, or morpholinyl;

and all other variables are as originally set forth in the first embodiment;

or a pharmaceutically acceptable salt thereof.

A feature of the sixteenth aspect is a compound of Formula (I), wherein R^3 is as defined in the sixteenth aspect, except that:

(i) HetC in the definition of R^3 is a saturated heterocyclic ring selected from piperidinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, isothiazolidinyl, oxazolidinyl, isooxazolidinyl, pyrrolidinyl, imidazolidinyl, piperazinyl, tetrahydrofuranyl, pyrazolidinyl, hexahydropyrimidinyl, thiazinanyl, thiazepanyl, thiadiazepanyl, dithiazepanyl, diazepanyl, and thiadiazinanyl, wherein the saturated heterocyclic ring is unsubstituted or substituted with 1 to 4 substituents each of which is independently:

(a) methyl or ethyl,
(b) =O,
(c) $-C(=O)N(R^aR^b)$,
(d) $-CH_2C(=O)N(R^aR^b)$,
(e) $-C(=O)R^a$, or
(f) $-SO_2R^c$; and

(ii) HetQ in the definition of R^3 is a bridged azabicycloalkyl selected from azabicyclo[2.2.1]cycloheptyl and azabicyclo[2.2.2]cyclooctyl; wherein the azabicycloalkyl is optionally substituted with from 1 to 4 substituents each of which is independently halogen, oxo, or C_{1-4} alkyl;

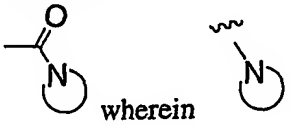
and all other variables are as originally set forth in the first embodiment;

or a pharmaceutically acceptable salt thereof.

A seventeenth aspect of the first embodiment is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^3 is restricted to one of groups (1) to (17) as set forth in the sixteenth aspect; and all other variables are as defined in the first aspect.

A feature of the seventeenth aspect is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^3 is as defined in the seventeenth aspect, except that HetC in the definition of R^3 is as defined in the preceding feature of the sixteenth aspect; and all other variables are as defined in the first aspect.

An eighteenth aspect of the first embodiment is a compound of Formula (I), wherein R^3 is:

(1) -H,
(2) $-C(=O)N(R^aR^b)$,
(3) $-CH_2-C(=O)N(R^aR^b)$,
(4) $-CH_2CH_2-C(=O)N(R^aR^b)$,
(5) $-S-CH_2-C(=O)N(R^aR^b)$,
(6) $-O-CH_2-C(=O)N(R^aR^b)$,
(7) $-N(SO_2R^c)-CH_2-C(=O)N(R^aR^b)$,
(8) $-N(R^a)-C(=O)-C(=O)-N(R^aR^b)$,
(9) $-N(R^a)SO_2R^c$,
(10) $-CH=CH-C(=O)-N(R^aR^b)$,
(11) $-N(R^a)-CH_2-C(=O)N(R^aR^b)$,
(12) $-N(R^a)-C(=O)-N(R^aR^b)$,
(13) -HetC,
(14) $-(CH_2)_{1-2}$ alkyl-HetC,
(15) $-N(R^a)-(CH_2)_{1-2}$-HetC,
(16) -HetQ, or
(17)  wherein is pyrrolidinyl or morpholinyl;

and all other variables are as originally defined in the first embodiment;

or a pharmaceutically acceptable salt thereof.

A feature of the eighteenth aspect is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^3 is as defined in the eighteenth aspect, except that:

(i) HetC in the definition of R^3 is a saturated heterocyclic ring selected from piperidinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, isothiazolidinyl, oxazolidinyl, isooxazolidinyl, pyrrolidinyl, imidazolidinyl, piperazinyl, tetrahydrofuranyl, pyrazolidinyl, hexahydropyrimidinyl, 1,2-thiazinanyl, 1,4-thiazepanyl, 1,2,5-thiadiazepanyl, 1,5,2-dithiazepanyl, 1,4-diazepanyl, and 1,2,6-thiadiazinanyl, wherein the saturated heterocyclic ring is unsubstituted or substituted with 1 to 4 substituents, each of which is independently:

(a) methyl or ethyl,
(b) =O,
(c) $-C(=O)NH_2$,
(d) $-C(=O)CH_3$, or
(e) $-SO_2CH_3$; and

(ii) HetQ in the definition of R^3 is a bridged azabicycloalkyl selected from azabicyclo[2.2.1]cycloheptyl and azabicyclo[2.2.2]cyclooctyl, wherein the azabicycloalkyl is optionally substituted with 1 or 2 substituents each of which is independently oxo or C_{1-4} alkyl;

and all other variables are as originally defined in the first embodiment;

or a pharmaceutically acceptable salt thereof.

A nineteenth aspect of the first embodiment is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^3 is restricted to one of groups (1) to (15) as set forth in the eighteenth aspect; and all other variables are as defined in the first aspect.

A feature of the nineteenth aspect is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^3 is as defined in the nineteenth aspect, except that HetC in the definition of R^3 is as defined in the preceding feature of the eighteenth aspect; and all other variables are as defined in the first aspect.

A twentieth aspect of the first embodiment is a compound of Formula (I), wherein R^3 is -H, -C(=O)N(R^aR^b), -N(R^a)SO_2R^c, -N(R^a)-C(=O)-C(=O)-N(R^aR^b), 1,1-dioxido-1,2-thiazinan-2-yl, 1,1-dioxidoisothiazolidin-2-yl, 1,1-dioxido-1,2,6-thiadiazinan-2-yl, 6-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl, or 3-oxo-2-azabicyclo[2.2.1]hept-2-yl;

and all other variables are as originally defined in the first embodiment;

or a pharmaceutically acceptable salt thereof.

A twenty-first aspect of the first embodiment is a compound of Formula (I), wherein R^3 is -H, -C(=O)N(R^aR^b), -N(R^a)SO_2R^c, or 1,1-dioxido-1,2-thiazinan-2-yl; and all other variables are as originally defined in the first aspect of the first embodiment; or a pharmaceutically acceptable salt thereof.

A twenty-second aspect of the first embodiment is a compound of Formula (I), wherein R^4 is -H; and all other variables are as originally defined in the first embodiment; or a pharmaceutically acceptable salt thereof.

A twenty-third aspect of the first embodiment is a compound of Formula (I), wherein R^4 is -H; and all other variables are as defined in the first aspect of the first embodiment; or a pharmaceutically acceptable salt thereof.

A twenty-fourth aspect of the first embodiment is a compound of Formula (I), wherein each R^a is independently -H, -C_{1-4} alkyl, -C_{1-4} haloalkyl, or cyclopropyl; each R^b is independently -H, -C_{1-4} alkyl, -C_{1-4} haloalkyl, or cyclopropyl; each R^c is independently a -C_{1-4} alkyl, -C_{1-4} haloalkyl, or cyclopropyl; and all other variables are as originally defined in the first embodiment; or a pharmaceutically acceptable salt thereof.

A twenty-fifth aspect of the first embodiment is a compound of Formula (I), wherein each R^a is independently -H, -C_{1-4} alkyl, -C_{1-4} haloalkyl, or cyclopropyl; each R^b is independently -H, -C_{1-4} alkyl, -C_{1-4} haloalkyl, or cyclopropyl; and each R^c is independently a -C_{1-4} alkyl, -C_{1-4} haloalkyl, or cyclopropyl; and all other variables are as defined in the first aspect; or a pharmaceutically acceptable salt thereof.

A feature of either the twenty-fourth or the twenty-fifth aspect is a compound of Formula (I), wherein

each R^a is independently -H, methyl, ethyl, -CF_3, or cyclopropyl;

each R^b is independently -H, methyl, ethyl, -CF_3, or cyclopropyl; and

each R^c is independently methyl, ethyl, -CF_3, or cyclopropyl;

and all other variables are as originally defined in the first embodiment or the first aspect thereof;

or a pharmaceutically acceptable salt thereof.

Another feature of either the twenty-fourth or the twenty-fifth aspect is a compound of Formula (I), wherein

each R^a is independently -H, methyl, or ethyl;

each R^b is independently -H, methyl, or ethyl; and

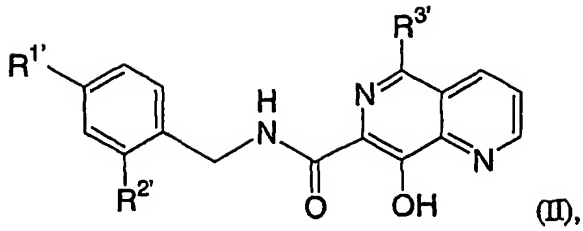
each R^c is independently methyl or ethyl;

and all other variables are as originally defined in the first embodiment or the first aspect thereof;

or a pharmaceutically acceptable salt thereof.

Additional aspects of the first embodiment of the present invention include, but are not limited to, compounds of Formula (I) wherein each of two or three or more of R^1, R^2, R^3, R^4, R^a, R^b, R^c HetA, HetB, and HetC is independently defined in accordance with its definition in one of the aspects, or a feature thereof, as set forth above. Any and all possible combinations of these variables in Formula (I) are additional aspects of the first embodiment of the present invention.

A second embodiment of the present invention is a compound of Formula (II):



(II),

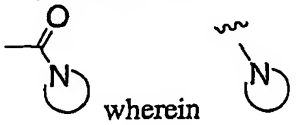
wherein

$R^{1'}$ is -H or -F;

$R^{2'}$ is

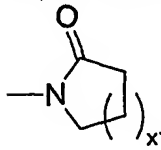
(1) $-C_{1-6}$ alkyl-C(=O)N(R^aR^b),

(2) -C(=O)N(R^aR^b),

(3)  wherein is azetidinyl, pyrrolidinyl, piperidinyl, or morpholino,

(4) triazolyl or tetrazolyl,

(5) -N(R^a)-C(R^b)=O,

(6)  wherein x1 is an integer equal to zero, 1, or 2, or

(7) $-CO_2R^c$;

$R^{3'}$ is:

(1) -H,

(2) -C(=O)N(R^aR^b),

(3) $-CH_2$-C(=O)N(R^aR^b),

(4) $-CH_2CH_2$-C(=O)N(R^aR^b),

(5) $-S-CH_2$-C(=O)N(R^aR^b),

(6) $-O-CH_2$-C(=O)N(R^aR^b),

(7) -N(R^a)-C(R^b)=O,

(8) -N(SO_2R^c)-CH_2-C(=O)N(R^aR^b),

(9) -N(R^a)-C(=O)-C(=O)-N(R^aR^b),

(10) $-N(R^a)SO_2R^c$,

(11) $-CH=CH-C(=O)-N(R^aR^b)$,

(12) $-N(R^a)-CH_2-C(=O)N(R^aR^b)$,

(13) $-N(R^a)-C(=O)-N(R^aR^b)$,

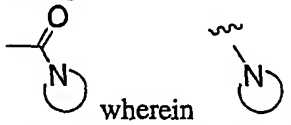
(14) -HetC',

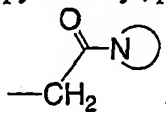
(15) $-(CH_2)_{1-3}$ alkyl-HetC',

(16) $-N(R^a)-(CH_2)_{1-3}$-HetC',

(17) $-N(R^a)-SO_2-N(R^aR^b)$,

(18) -HetQ',

(19)  wherein is as defined above in $R^{2'}$ (i.e., azetidinyl, pyrrolidinyl, piperidinyl, or morpholinyl), or

(20)  wherein  is as defined above in $R^{2'}$;

HetC' is a 5- to 7-membered saturated heterocyclic ring containing from 1 to 4 heteratoms independently selected from N, O and S, wherein the saturated heterocyclic ring is optionally substituted with from 1 to 4 substituents each of which is independently halogen, $-C_{1-4}$ alkyl, $-C_{3-6}$ cycloalkyl, $-O-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-O-C_{1-4}$ haloalkyl, -CN, oxo, phenyl, benzyl, phenylethyl, $-(CH_2)_{0-3}C(=O)N(R^aR^b)$, $-(CH_2)_{0-3}C(=O)R^a$, $-N(R^a)-C(=O)R^b$, $-N(R^a)-CO_2R^b$, $-(CH_2)_{1-3}N(R^a)-C(=O)R^b$, $-N(R^aR^b)$, $-(CH_2)_{1-3}N(R^aR^b)$, $-SO_2R^c$, $-(CH_2)_{0-3}C(=O)$-HetD', -HetD', $-N(R^a)$-HetD', and $-(CH_2)_{1-3}$-HetD'; wherein each HetD' is independently a 5- or 6-membered heteroaromatic ring containing from 1 to 4 nitrogen atoms or a 5- or 6-membered saturated heterocyclic ring containing from 1 to 4 nitrogen atoms, wherein the ring is optionally substituted with 1 or 2 substituents each of which is independently halogen, oxo, $-C_{1-4}$ alkyl, or $-O-C_{1-4}$ alkyl;

HetQ' is a 7- to 9-membered bridged azabicycloalkyl saturated ring system containing a C_{5-7} azacycloalkyl ring in which two of the ring carbons are connected by a bridge containing 1 or 2 carbon atoms; wherein the bridged azabicycloalkyl ring system is optionally substituted with from 1 to 4 substituents each of which is independently halogen, oxo, or $-C_{1-4}$ alkyl;

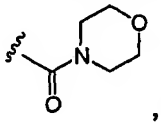
each R^a is independently -H, -C_{1-6} alkyl, or -C_{3-6} cycloalkyl;

each R^b is independently -H, -C_{1-6} alkyl, or -C_{3-6} cycloalkyl; and

each R^c is independently a -C_{1-6} alkyl or -C_{3-6} cycloalkyl;

or a pharmaceutically acceptable salt thereof.

A first aspect of the second embodiment of the present invention is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein $R^{2'}$ is restricted to one of groups (1) to (3); $R^{3'}$ is restricted to one of groups (1) to (17); and all other variables are as defined in the second embodiment.

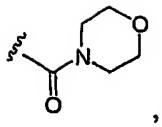
A second aspect of the second embodiment of the present invention is a compound of Formula (II), wherein $R^{2'}$ is -$(CH_2)_{1-3}$-C(=O)N(R^aR^b), -C(=O)N(R^aR^b),  , triazolyl, or tetrazolyl;

and all other variables are as originally defined in the second embodiment;

or a pharmaceutically acceptable salt thereof.

A third aspect of the second embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein $R^{2'}$ is -$(CH_2)_{1-3}$-C(=O)N(R^aR^b) or -C(=O)N(R^aR^b); and all other variables are as defined in the first aspect of the second embodiment.

A fourth aspect of the second embodiment of the present invention is a compound of Formula (II), wherein

$R^{2'}$ is $-(CH_2)_{1-3}-C(=O)N(R^{a*}R^{b*})$, $-C(=O)N(R^{a*}R^{b*})$,  , triazolyl, or tetrazolyl;

R^{a*} and R^{b*} are each independently -H, $-C_{1-4}$ alkyl, or cyclopropyl, with the proviso that R^{a*} and R^{b*} are not both -H;

each R^a in $R^{3'}$ is independently -H, $-C_{1-4}$ alkyl, or cyclopropyl;

each R^b in $R^{3'}$ is independently -H, $-C_{1-4}$ alkyl, or cyclopropyl; and

each R^c in $R^{3'}$ is independently a $-C_{1-4}$ alkyl or cyclopropyl;

and all other variables are as originally defined in the second embodiment;

or a pharmaceutically acceptable salt thereof.

In a feature of the fourth aspect of the second embodiment, one of R^{a*} and R^{b*} is -H, and the other of R^{a*} and R^{b*} is $-C_{1-4}$ alkyl or cyclopropyl; and all other variables are as defined in the fourth aspect.

A fifth aspect of the second embodiment of the present invention is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein

$R^{2'}$ is $-(CH_2)_{1-3}-C(=O)N(R^{a*}R^{b*})$ or $-C(=O)N(R^{a*}R^{b*})$;

R^{a*} and R^{b*} are each independently -H, $-C_{1-4}$ alkyl, or cyclopropyl, with the proviso that R^{a*} and R^{b*} are not both -H;

each R^a in $R^{3'}$ is independently -H, $-C_{1-4}$ alkyl, or cyclopropyl;

each R^b in $R^{3'}$ is independently -H, $-C_{1-4}$ alkyl, or cyclopropyl; and

each R^c in $R^{3'}$ is independently a -C_{1-4} alkyl or cyclopropyl;

and all other variables are as originally defined in the first aspect of the second embodiment;

or a pharmaceutically acceptable salt thereof.

In a feature of the fifth aspect of the second embodiment, one of R^{a*} and R^{b*} is -H, and the other of R^{a*} and R^{b*} is -C_{1-4} alkyl or cyclopropyl; and all other variables are as set forth in the fifth aspect.

A sixth aspect of the second embodiment of the present invention is a compound of Formula (II), wherein

HetC' in the definition of $R^{3'}$ is a saturated heterocyclic ring selected from piperidinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, isothiazolidinyl, oxazolidinyl, isooxazolidinyl, pyrrolidinyl, imidazolidinyl, piperazinyl, tetrahydrofuranyl, pyrazolidinyl, hexahydropyrimidinyl, thiazinanyl, thiazepanyl, thiadiazepanyl, dithiazepanyl, diazepanyl, and thiadiazinanyl, wherein the saturated heterocyclic ring is unsubstituted or substituted with 1 to 4 substituents each of which is independently:

(a) methyl or ethyl,
(b) =O,
(c) -C(=O)N(R^aR^b),
(d) -CH_2C(=O)N(R^aR^b),
(e) -C(=O)R^a, or
(f) -SO_2R^c;

and all other variables are as originally defined in the second embodiment;

or a pharmaceutically acceptable salt thereof.

A seventh aspect of the second embodiment of the present invention is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein HetC' in the definition of $R^{3'}$ is as defined in the sixth aspect of the second

embodiment; and all other variables are as defined in the first aspect of the second embodiment.

An eighth aspect of the second embodiment of the present invention is a compound of Formula (II), wherein $R^{3'}$ is:

-H, -C(=O)N(R^aR^b), -N(R^a)SO_2R^c, -N(R^a)-C(=O)-C(=O)-N(R^aR^b), 1,1-dioxido-1,2-thiazinan-2-yl, 1,1-dioxidoisothiazolidin-2-yl, 1,1-dioxido-1,2,6-thiadiazinan-2-yl, 6-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl, or 3-oxo-2-azabicyclo[2.2.1]hept-2-yl;

and all other variables are as originally defined in the second embodiment;

or a pharmaceutically acceptable salt thereof.

A ninth aspect of the second embodiment of the present invention is a compound of Formula (II), wherein $R^{3'}$ is:

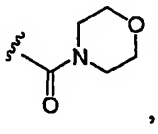
-H, -C(=O)N(R^aR^b), -N(R^a)SO_2R^c, or 1,1-dioxido-1,2-thiazinan-2-yl;

and all other variables are as originally defined in the first aspect of the second embodiment;

or a pharmaceutically acceptable salt thereof.

A tenth aspect of the second embodiment of the present invention is a compound of Formula (II), wherein

$R^{1'}$ is -H or -F;

$R^{2'}$ is -$(CH_2)_{1-3}$-C(=O)N($R^{a*}R^{b*}$), -C(=O)N($R^{a*}R^{b*}$),  , triazolyl, or tetrazolyl;

R^{a*} and R^{b*} are each independently -H, -C_{1-4} alkyl, or cyclopropyl, with the proviso that R^{a*} and R^{b*} are not both -H;

$R^{3'}$ is -H, -C(=O)N(R^aR^b), -N(R^a)SO_2R^c, -N(R^a)-C(=O)-C(=O)-N(R^aR^b), 1,1-dioxido-1,2-thiazinan-2-yl, 1,1-dioxidoisothiazolidinyl-2-yl, 1,1-dioxido-1,2,6-thiadiazinan-2-yl; or 3-oxo-2-azabicyclo[2.2.1]hept-2-yl;

R^a and R^b are each independently -H, -C_{1-4} alkyl, or cyclopropyl, with the proviso that R^a and R^b are not both -H; and

R^c is -C_{1-4} alkyl or cyclopropyl;

or a pharmaceutically acceptable salt thereof.

An eleventh aspect of the second embodiment of the present invention is a compound of Formula (II), wherein

$R^{1'}$ is -H or -F;

$R^{2'}$ is -$(CH_2)_{1-3}$-C(=O)N($R^{a*}R^{b*}$) or -C(=O)N($R^{a*}R^{b*}$);

R^{a*} and R^{b*} are each independently -H, -C_{1-4} alkyl, or cyclopropyl, with the proviso that R^{a*} and R^{b*} are not both -H;

$R^{3'}$ is -H, -C(=O)N(R^aR^b), -$NHSO_2R^c$, -N(-C_{1-4} alkyl)SO_2R^c, or 1,1-dioxido-1,2-thiazinan-2-yl;

R^a and R^b are each independently -H, -C_{1-4} alkyl, or cyclopropyl, with the proviso that R^a and R^b are not both -H; and

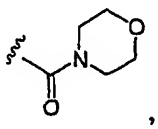
R^c is -C_{1-4} alkyl or cyclopropyl;

or a pharmaceutically acceptable salt thereof.

In a feature of either the tenth or the eleventh aspect of the second embodiment, R^{a*} and R^{b*} are each independently -H, methyl, ethyl, or cyclopropyl, with the proviso that R^{a*} and R^{b*} are not both -H; and R^a and R^b are each independently -H, methyl, ethyl, or cyclopropyl, with the proviso that R^a and R^b are not both -H; and R^c is methyl, ethyl, or cyclopropyl.

A twelfth aspect of the second embodiment of the present invention is a compound of Formula (II), wherein

$R^{1'}$ is -H or -F;

$R^{2'}$ is $-(CH_2)_{1-3}-C(=O)N(R^{a*}R^{b*})$, $-C(=O)N(R^{a*}R^{b*})$,  , triazolyl, or tetrazolyl;

one of R^{a*} and R^{b*} is -H, and the other of R^{a*} and R^{b*} is $-C_{1-4}$ alkyl or cyclopropyl;

$R^{3'}$ is -H, $-C(=O)N(R^aR^b)$, $-N(R^a)SO_2R^c$, $-N(R^a)-C(=O)-C(=O)-N(R^aR^b)$, 1,1-dioxido-1,2-thiazinan-2-yl, 1,1-dioxidoisothiazolidinyl-2-yl, 1,1-dioxido-1,2,6-thiadiazinan-2-yl; or 3-oxo-2-azabicyclo[2.2.1]hept-2-yl;

R^a and R^b are each independently -H, $-C_{1-4}$ alkyl, or cyclopropyl, with the proviso that R^a and R^b are not both -H; and

R^c is $-C_{1-4}$ alkyl or cyclopropyl;

or a pharmaceutically acceptable salt thereof.

A thirteenth aspect of the second embodiment of the present invention is a compound of Formula (II), wherein

$R^{1'}$ is -H or -F;

$R^{2'}$ is $-(CH_2)_{1-3}-C(=O)N(R^{a*}R^{b*})$ or $-C(=O)N(R^{a*}R^{b*})$;

one of R^{a*} and R^{b*} is -H, and the other of R^{a*} and R^{b*} is -C_{1-4} alkyl or cyclopropyl;

$R^{3'}$ is -H, -C(=O)N(R^aR^b), -$NHSO_2R^c$, -N(-C_{1-4} alkyl)SO_2R^c, or 1,1-dioxido-1,2-thiazinan-2-yl;

R^a and R^b are each independently -H, -C_{1-4} alkyl, or cyclopropyl, with the proviso that R^a and R^b are not both -H; and

R^c is -C_{1-4} alkyl or cyclopropyl;

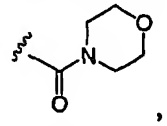
or a pharmaceutically acceptable salt thereof.

In a feature of either the twelfth or the thirteenth aspect, one of R^{a*} and R^{b*} is -H, and the other of R^{a*} and R^{b*} is -C_{1-4} alkyl or cyclopropyl. In another feature of either the twelfth or the thirteenth aspect, one of R^{a*} and R^{b*} is -H, and the other of R^{a*} and R^{b*} is methyl, ethyl, isopropyl, or n-propyl.

A fourteenth aspect of the second embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein

$R^{1'}$ is -H or -F;

$R^{2'}$ is

(1) -$(CH_2)_{1-3}$-C(=O)N($R^{a*}R^{b*}$),
(2) -C(=O)N($R^{a*}R^{b*}$),
(3) -$C(=O)NH_2$,
(4)  ,
(5) triazolyl, or
(6) tetrazolyl;

$R^{3'}$ is:

(1) -H,

(2) $-C(=O)N(R^{a"}R^{b"})$,
(3) $-CH_2-C(=O)N(R^{a"}R^{b"})$,
(4) $-CH_2CH_2-C(=O)N(R^{a"}R^{b"})$,
(5) $-N(R^a)-C(R^b)=O$,
(6) $-N(R^a)-C(=O)-C(=O)-N(R^aR^b)$,
(7) $-N(R^a)SO_2R^c$,
(8) -HetC', or
(9) -HetQ';

HetC' is a saturated heterocyclic ring selected from thiazinanyl, isothiazolidinyl, and thiadiazinanyl, wherein the saturated heterocyclic ring is optionally substituted with from 1 to 4 substituents each of which is independently $-C_{1-4}$ alkyl or oxo;

HetQ' is azabicyclo[2.2.1]heptyl optionally substituted with 1 or 2 substituents each of which is independently oxo or $-C_{1-4}$ alkyl;

one of R^{a*} and R^{b*} is -H, $-C_{1-4}$ alkyl; or cyclopropyl, and the other of R^{a*} and R^{b*} is $-C_{1-4}$ alkyl or cyclopropyl;

each of $R^{a"}$ and $R^{b"}$ is independently $-C_{1-4}$ alkyl or cyclopropyl;

each of R^a and R^b is independently -H, $-C_{1-4}$ alkyl, or cyclopropyl; and

R^c is $-C_{1-4}$ alkyl or cyclopropyl;

or a pharmaceutically acceptable salt thereof.

A feature of the fourteenth aspect of the second embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein $R^{2'}$ and $R^{3'}$ are as defined in the fourteenth aspect; one of R^a and R^b is -H, $-C_{1-4}$ alkyl, or cyclopropyl, and the other of R^a and R^b is $-C_{1-4}$ alkyl or cyclopropyl; all other variables are as defined in the fourteenth aspect; and provided that:

(i) when $R^{3'}$ is $-C(=O)N(R^{a"}R^{b"})$, $-CH_2-C(=O)N(R^{a"}R^{b"})$, or $-CH_2CH_2-C(=O)N(R^{a"}R^{b"})$, then $R^{2'}$ is not $-C(=O)NH_2$; and

(ii) when $R^{3'}$ is $-N(R^a)-C(R^b)=O$ or $-N(R^a)-C(=O)-C(=O)-N(R^aR^b)$, then $R^{2'}$ is not $-C(=O)N(R^{a*}R^{b*})$ or $-(CH_2)_{1-3}-C(=O)N(R^{a*}R^{b*})$ wherein both R^{a*} and R^{b*} are not H.

A fifteenth aspect of the second embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein

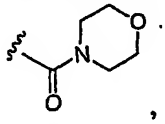
$R^{1'}$ is -H or -F;

$R^{2'}$ is:

(1) $-CH_2C(=O)N(R^{a*}R^{b*})$,

(2) $-C(=O)N(R^{a*}R^{b*})$,

(3) $-C(=O)NH_2$,

(4)  ,

(5) triazolyl, or

(6) tetrazolyl;

$R^{3'}$ is:

(1) $-C(=O)N(R^{a''}R^{b''})$,

(2) $-CH_2-C(=O)N(R^{a''}R^{b''})$,

(3) $-CH_2CH_2-C(=O)N(R^{a''}R^{b''})$,

(4) $-N(R^a)-C(R^b)=O$,

(5) $-N(R^a)-C(=O)-C(=O)-N(R^aR^b)$,

(6) $-N(R^a)SO_2R^c$,

(7) 1,1-dioxido-1,2-thiazinan-2-yl,

(8) 1,1-dioxidoisothiazolidin-2-yl,

(9) 1,1-dioxido-1,2,6-thiadiazinan-2-yl,

(10) 6-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl, or

(11) 3-oxo-2-azabicyclo[2.2.1]hept-2-yl;

one R^{a*} and R^{b*} is -H, $-C_{1-3}$ alkyl, or cyclopropyl, and the other of R^{a*} and R^{b*} is $-C_{1-3}$ alkyl;

each of $R^{a"}$ and $R^{b"}$ is independently a -C_{1-3} alkyl;

each of R^a and R^b is independently a -C_{1-3} alkyl; and

R^c is -C_{1-3} alkyl.

A feature of the fifteenth aspect of the second embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein $R^{2'}$ and $R^{3'}$ are as defined in the fifteenth aspect; all other variables are as defined in the fifteenth aspect; and provided that:

(i) when $R^{3'}$ is -C(=O)N($R^{a"}R^{b"}$), -CH_2-C(=O)N($R^{a"}R^{b"}$), or -CH_2CH_2-C(=O)N($R^{a"}R^{b"}$), then $R^{2'}$ is not -C(=O)NH_2; and

(ii) when $R^{3'}$ is -N(R^a)-C(R^b)=O or -N(R^a)-C(=O)-C(=O)-N(R^aR^b), then $R^{2'}$ is not -C(=O)N($R^{a*}R^{b*}$) or -$(CH_2)_{1-3}$-C(=O)N($R^{a*}R^{b*}$) wherein both R^{a*} and R^{b*} are not H.

A sixteenth aspect of the second embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein

$R^{1'}$ is -H or -F;

$R^{2'}$ is:

(1) -CH_2C(=O)NH(CH_3),

(2) -CH_2C(=O)N(CH_3)$_2$,

(3) -C(=O)NH(CH_3),

(4) -C(=O)N(CH_3)$_2$,

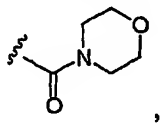
(5) -C(=O)NH(CH_2CH_3),

(6) -C(=O)NH($CH_2CH_2CH_3$),

(7) -C(=O)NH(CH(CH_3)$_2$),

(8) -CH_2C(=O)NH(cyclopropyl),

(9) -C(=O)NH_2,

(10)  ,

(11) triazolyl, or
(12) tetrazolyl; and

$R^{3'}$ is:
(1) $-C(=O)N(CH_3)_2$,
(2) $-N(CH_3)-C(CH_3)=O$,
(3) $-N(CH_3)-C(=O)-C(=O)-N(CH_3)_2$,
(4) $-N(CH_3)SO_2CH_3$,
(5) $-N(CH_3)SO_2CH_2CH_3$,
(6) $-N(CH_2CH_3)SO_2CH_3$,
(7) 1,1-dioxido-1,2-thiazinan-2-yl,
(8) 1,1-dioxidoisothiazolidin-2-yl,
(9) 6-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl, or
(10) 3-oxo-2-azabicyclo[2.2.1]hept-2-yl;
provided that:
(i) when $R^{3'}$ is $-C(=O)N(CH_3)_2$, then $R^{2'}$ is not $-C(=O)NH_2$; and
(ii) when $R^{3'}$ is $-N(CH_3)-C(CH_3)=O$ or $-N(CH_3)-C(=O)-C(=O)-N(CH_3)_2$, then $R^{2'}$ is not $-C(=O)N(CH_3)_2$ or $-CH_2C(=O)N(CH_3)_2$.

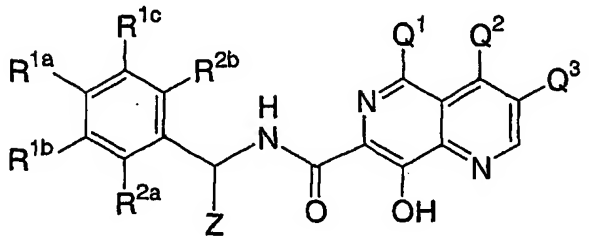
A feature of the sixteenth aspect is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein:

$R^{2'}$ is $-C(=O)NH_2$, $-C(=O)NH(CH_3)$, $-C(=O)N(CH_3)_2$, or $-C(=O)NH(CH_2CH_3)$; and

$R^{3'}$ is $-N(CH_3)SO_2CH_3$, $-N(CH_3)SO_2CH_2CH_3$, 1,1-dioxido-1,2-thiazinan-2-yl, or 6-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl.

Additional aspects of the second embodiment of the present invention include, but are not limited to, compounds of Formula (II) wherein each of two or three or more of $R^{1'}$, $R^{2'}$, $R^{3'}$, R^a, R^b, R^c and HetC' is independently defined in accordance with its definition in one of the aspects, or a feature thereof, as set forth above. Any and all possible combinations of these variables in Formula (II) are additional aspects of the second embodiment of the present invention.

A third embodiment of the present invention is a compound of Formula (III):



(III),

wherein

R^{1a}, R^{1b}, and R^{1c} are each independently -H, halogen, -C_{1-6} alkyl, -C_{3-6} cycloalkyl, or -C_{1-6} haloalkyl;

R^{2a} and R^{2b} are each independently:

(1) -H,

(2) -C_{1-6} alkyl substituted with from 1 to 3 substituents each of which is independently -CN, -NO_2, -OCO_2R^c, -$S(=O)R^c$, -SO_2R^c, -$SO_2N(R^aR^b)$, -$N(R^a)CO_2R^c$, -$N(R^a)SO_2R^c$, -$N(R^a)SO_2N(R^aR^b)$, -$OC(=O)N(R^aR^b)$, or -$N(R^a)C(=O)N(R^aR^b)$;

(3) -O-C_{1-6} alkyl substituted with from 1 to 3 substituents each of which is independently -$S(=O)R^c$, -SO_2R^c, -$C(=O)N(R^aR^b)$, -$SO_2N(R^aR^b)$, -$N(R^a)C(=O)R^b$, -$N(R^a)SO_2R^c$, -$N(R^a)SO_2N(R^aR^b)$, -$OC(=O)N(R^aR^b)$, or -$N(R^a)C(=O)N(R^aR^b)$,

(4) -$SO_2N(R^aR^b)$,

(5) -$N(R^a)S(=O)R^c$,

(6) -$OC(=O)N(R^aR^b)$,

(7) -$N(R^a)C(=O)N(R^aR^b)$,

(8) -$N(R^a)$-C_{1-6} alkyl-$C(=O)N(R^aR^b)$,

(9) -$N(R^a)$-$C(=O)$-C_{1-6} alkyl-$N(R^aR^b)$,

(10) -$N(R^a)C(=O)$-$C(=O)N(R^aR^b)$,

(11) -OCO_2R^c,

(12) -$N(R^a)$-$SO_2N(R^aR^b)$,

(13) -$N(R^a)$-SO_2-C_{1-6} alkyl-$N(R^aR^b)$,

(14) -$N(R^a)C(=O)R^b$,

(15) $-N(R^a)CO_2R^c$,
(16) $-S-C_{1-6}$ alkyl-$C(=O)N(R^aR^b)$,
(17) $-N(SO_2R^c)-C_{1-6}$ alkyl-$C(=O)N(R^aR^b)$,
(18) $-N(R^a)-C(=O)-C_{1-6}$ alkyl-$C(=O)N(R^aR^b)$,
(19) $-N(R^a)-C(=O)-C_{1-6}$ alkyl-$N(R^a)C(=O)(R^b)$,
(20) $-N(R^a)-SO_2-C_{1-6}$ alkyl-$C(=O)N(R^aR^b)$,
(21) $-N(R^a)-SO_2-C_{1-6}$ alkyl-$N(R^a)C(=O)(R^b)$,
(22) $-C(=O)N(R^a)-C_{1-6}$ alkyl-$C(=O)N(R^aR^b)$, or
(23) $-C(=O)N(R^a)-C_{1-6}$ alkyl-$N(R^a)C(=O)(R^b)$, with the proviso that the -N(Ra)- moieties are not both attached to the same carbon atom of the $-C_{1-6}$ alkyl- moiety,
(24) $-C(=O)N(R^a)-C_{1-6}$ alkyl-$O-C_{1-3}$ alkyl, with the proviso that the -N(Ra)- moiety and the $-O-C_{1-3}$ alkyl group are not both attached to the same carbon atom of the $-C_{1-6}$ alkyl- moiety, or
(25) $-C(=O)N(R^a)-C_{1-6}$ alkyl-$S(O)_nR^c$;

with the proviso that at least one of R^{2a} and R^{2b} is other than -H;

Q^1 is

(1) -H,
(2) $-C_{1-6}$ alkyl, optionally substituted with from 1 to 4 substituents each of which is independently -OH, $-O-C_{1-6}$ alkyl, $-O-C_{1-6}$ haloalkyl, -CN, $-NO_2$, $-N(R^aR^b)$, $-C(=O)N(R^aR^b)$, $-OC(=O)N(R^aR^b)$, $-N(R^a)C(=O)N(R^aR^b)$, $-N(R^a)-C_{1-6}$ alkyl-$C(=O)N(R^aR^b)$, $-N(R^a)-C(=O)-C_{1-6}$ alkyl-$N(R^aR^b)$, $-N(R^a)C(=O)-C(=O)N(R^aR^b)$, $-C(=O)R^a$, $-CO_2R^c$, $-OCO_2R^c$, $-S(O)_nR^c$, $-SO_2N(R^aR^b)$, $-N(R^a)-SO_2N(R^aR^b)$, $-N(R^a)-SO_2-C_{1-6}$ alkyl-$N(R^aR^b)$, $-N(R^a)C(=O)R^b$, $-N(R^a)CO_2R^c$, $-N(R^a)SO_2R^c$, or -G-C_{1-6} alkyl-$C(=O)N(R^aR^b)$ wherein G is O or S or $N(SO_2R^c)$,
(3) $-C_{1-6}$ haloalkyl,
(4) $-O-C_{1-6}$ alkyl,
(5) $-O-C_{1-6}$ haloalkyl,
(6) halo,
(7) -CN,

(8) $-S(O)_nR^c$,

(9) $-SO_2N(R^aR^b)$,

(10) $-N(R^aR^b)$,

(11) $-C(=O)N(R^aR^b)$,

(12) $-N(R^a)-C(=O)R^b$,

(13) $-N(R^a)SO_2R^c$,

(14) $-G-(CH_2)_{1-2}-C(=O)N(R^aR^b)$, wherein G is O, S, or $N(SO_2R^c)$,

(15) $-C(=O)-N(R^a)-(CH_2)_{1-3}-[C(=O)]_{0-1}-N(R^aR^b)$,

(16) $-C(=O)-N(R^a)-(CH_2)_{1-2}H$ substituted with 1 or 2 $-O-C_{1-6}$ alkyl,

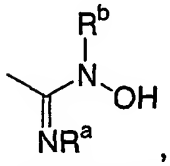
(17) $-CH=CH-(CH_2)_{0-1}-C(=O)-N(R^a)_2$,

(18) $—C\equiv C-CH_2OR^a$,

(19) $—C\equiv C-CH_2SR^c$,

(20) $—C\equiv C-CH_2SO_2R^c$,

(21) $—C\equiv C-CH_2N(R^aR^b)$,

(22)  ,

(23) $-N(R^a)-(CH_2)_{1-4}-S(O)_nR^c$,

(24) $-N(R^a)-(CH_2)_{1-4}-O-C_{1-6}$ alkyl,

(25) $-N(R^a)-(CH_2)_{1-4}-N(R^aR^b)$,

(26) $-N(R^a)-(CH_2)_{1-4}N(R^a)-C(=O)R^b$,

(27) $-N(R^a)-(CH_2)_{0-2}-[C(=O)]_{1-2}N(R^aR^b)$,

(28) $-N(R^a)-(CH_2)_{1-4}-CO_2R^c$,

(29) $-N(R^a)C(=O)N(R^a)-(CH_2)_{1-4}-C(=O)N(R^aR^b)$,

(30) $-N(R^a)C(=O)-(CH_2)_{1-4}-N(R^aR^b)$,

(31) $-N(R^a)-SO_2-N(R^aR^b)$,

(32) $-R^k$,

(33) $-C_{1-6}$ alkyl substituted with one of:

(i) $-R^k$,

(ii) $-S(O)_n-R^k$,

(iii) $-S(O)_n-C_{1-6}$ alkyl-R^k,

(iv) $-C(=O)-R^k$,

(v) $-C(=O)-C_{1-6}$ alkyl-R^k,

(vi) -C(=O)N(R^a)-R^k,
(vii) -C(=O)N(R^a)-C_{1-6} alkyl-R^k,
(viii) -O-R^k,
(ix) -O-C_{1-6} alkyl-R^k,
(x) -N(R^a)-R^k,
(xi) -N(R^a)-C_{1-6} alkyl-R^k,
(xii) -N(R^a)C(=O)-R^k, or
(xiii) -N(R^a)C(=O)-C_{1-6} alkyl-R^k,

(34) -C_{2-6} alkenyl, optionally substituted with -R^k,
(35) -C_{2-5} alkynyl, optionally substituted with -R^k,
(36) -O-R^k,
(37) -C(=O)-R^k,
(38) -C(=O)-C_{1-6} alkyl-R^k,
(39) -N(R^a)-R^k,
(40) -N(R^a)C(=O)-R^k,
(41) -N(R^a)C(=O)-C_{1-6} alkyl-R^k, or
(42) -$S(O)_n$-C_{1-6} alkyl-R^k;

R^k is a carbocycle or a heterocycle;

carbocycle in R^k is independently (i) a C_3 to C_8 monocyclic, saturated or unsaturated ring, (ii) a C_7 to C_{12} bicyclic ring system, or (iii) a C_{11} to C_{16} tricyclic ring system, wherein each ring in (ii) or (iii) is independent of, bridged with, or fused to the other ring or rings (alternatively, the ring systems are restricted to those wherein each ring in (ii) or (iii) is independent of or fused to the other ring or rings) and each ring is saturated or unsaturated; wherein the carbocycle is optionally substituted with from 1 to 7 substituents each of which is independently

(1) halogen,
(2) -OH,
(3) -C_{1-6} alkyl, optionally substituted with from 1 to 4 substituents each of which is independently -OH, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, -CN, -NO_2, -N(R^aR^b), -C(=O)N(R^aR^b), -C(=O)R^a, -CO_2R^c, -OCO_2R^c, -$S(O)_nR^c$, -SO_2N(R^aR^b), -N(R^a)SO_2R^c, -N(R^a)C(=O)R^b, -N(R^a)CO_2R^c, -N(R^a)SO_2R^c, phenyl, -O-phenyl, or HetX,

(4) -C_{1-6} haloalkyl,
(5) -O-C_{1-6} alkyl,
(6) -O-C_{1-6} haloalkyl,
(7) -CN,
(8) -NO_2,
(9) -$N(R^aR^b)$,
(10) -$C(=O)N(R^aR^b)$,
(11) -$C(=O)R^a$,
(12) -CO_2R^c,
(13) -OCO_2R^c,
(14) -$S(O)_nR^c$,
(15) -$N(R^a)SO_2R^c$,
(16) -$SO_2N(R^aR^b)$,
(17) -$N(R^a)C(=O)R^b$,
(18) -$N(R^a)CO_2R^c$,
(19) -C_{3-6} cycloalkyl,
(20) phenyl,
(21) -O-phenyl, or
(22) HetX,

wherein each HetX is independently a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally fused with a benzene ring; and wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, oxo, or -CO_2R^c;

heterocycle in R^k is independently (i) a 4- to 8-membered, saturated or unsaturated monocyclic ring, (ii) a 7- to 12-membered bicyclic ring system, or (iii) an 11 to 16-membered tricyclic ring system; wherein each ring in (ii) or (iii) is independent of, bridged with, or fused to the other ring or rings (alternatively, the ring systems are restricted to those wherein each ring in (ii) or (iii) is independent of or fused to the other ring or rings) and each ring is saturated or unsaturated; the monocyclic ring, bicyclic ring system, or tricyclic ring system contains from 1 to 6 heteroatoms

independently selected from N, O and S; and wherein any one or more of the nitrogen and sulfur heteroatoms is optionally oxidized, and any one or more of the nitrogen heteroatoms is optionally quaternized; wherein the heterocycle is optionally substituted with from 1 to 7 substituents each of which is independently

(1) halogen,
(2) -OH,
(3) -C_{1-6} alkyl, optionally substituted with one or more substituents each of which is independently -OH, -O-C_{1-6} alkyl, -CN, -NO_2, -$N(R^aR^b)$, -$C(=O)N(R^aR^b)$, -$C(=O)R^a$, -CO_2R^c, -$S(O)_nR^c$, -$N(R^a)SO_2R^c$, -$SO_2N(R^aR^b)$, -$N(R^a)C(=O)R^b$, -$N(R^a)CO_2R^c$, phenyl, -O-phenyl, HetY, or -C(=O)-HetY,
(4) -C_{1-6} haloalkyl,
(5) -O-C_{1-6} alkyl,
(6) -O-C_{1-6} haloalkyl,
(7) -CN,
(8) -NO_2,
(9) -$N(R^aR^b)$,
(10) -$C(=O)N(R^aR^b)$,
(11) -$C(=O)R^a$,
(12) -CO_2R^c,
(13) -OCO_2R^c,
(14) -$S(O)_nR^c$,
(15) -$N(R^a)SO_2R^c$,
(16) -$SO_2N(R^aR^b)$,
(17) -$N(R^a)C(=O)R^b$,
(18) -$N(R^a)CO_2R^c$,
(19) -C_{3-6} cycloalkyl,
(20) -phenyl,
(21) -O-phenyl,
(22) HetY,
(23) -$N(R^a)$-HetY, or
(24) oxo;

wherein each HetY is independently

(1) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S,

wherein the heteroaromatic ring is optionally fused with a benzene ring; or

(2) a 5- or 6-membered saturated heterocyclic ring containing from 1 to 4 heteroatoms independently selected from N, O and S;

wherein the heteroaromatic ring or the saturated heterocyclic ring is optionally substituted with from 1 to 7 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, oxo, or -CO_2R^c; and

each of Q^2 and Q^3 is independently

(1) -H,

(2) -C_{1-6} alkyl, optionally substituted with from 1 to 4 substituents each of which is independently -OH, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, -CN, -NO_2, -$N(R^aR^b)$, -$C(=O)N(R^aR^b)$, -$C(=O)R^a$, -CO_2R^c, -OCO_2R^c, -$S(O)_nR^c$, -$SO_2N(R^aR^b)$, -$N(R^a)C(=O)R^b$, -$N(R^a)CO_2R^c$, -$N(R^a)SO_2R^c$, or -$N(R^a)SO_2N(R^aR^b)$, or

(3) -C_{1-6} haloalkyl;

Z is -H or -$C(=O)N(R^aR^b)$;

each R^a is independently -H, -C_{1-6} alkyl, -C_{1-6} haloalkyl, or -C_{3-6} cycloalkyl;

each R^b is independently -H, -C_{1-6} alkyl, -C_{1-6} haloalkyl, or -C_{3-6} cycloalkyl;

each R^c is independently -C_{1-6} alkyl, -C_{1-6} haloalkyl, or -C_{3-6} cycloalkyl; and

each n is independently an integer equal to zero, 1, or 2;

or a pharmaceutically acceptable salt thereof.

A first aspect of the third embodiment of the present invention is a compound of Formula (III), wherein R^k is -C_{3-8} cycloalkyl, -C_{7-12} fused bicyclic carbocycle in which at least one of the rings is non-aromatic, aryl, heteroaryl, a 4- to 7-membered saturated heterocyclic ring containing from 1 to 4 heteratoms selected

from N, O and S, or a C_{5-7} azacycloalkyl ring in which two of the ring carbons are connected by a bridge containing 1 or 2 carbon atoms;

wherein the cycloalkyl, the fused bicyclic carbocycle or the aryl is optionally substituted with from 1 to 5 substituents each of which is independently one of substituents (1) to (22) set forth in the third embodiment as substituents when R^k is a carbocycle; and

wherein the heteroaryl, the saturated heterocyclic ring, or the bridged azacycloalkyl is optionally substituted with from 1 to 5 substituents each of which is independently one of substituents (1) to (24) set forth in the third embodiment as substituents when R^k is a heterocycle;

and all other variables are as defined in the third embodiment;

or a pharmaceutically acceptable salt thereof.

A second aspect of the third embodiment of the present invention is a compound of Formula (III), or a pharmaceutically acceptable salt thereof, wherein R^k is as defined in the first aspect except that R^k is not a bridged C_{5-7} azacycloalkyl ring; and all other variables are as defined in the third embodiment.

A third aspect of the third embodiment of the present invention is a compound of Formula (III), wherein R^k is:

(i) -C_{3-8} cycloalkyl, which is optionally substituted with from 1 to 3 substituents each of which is independently halogen, -C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, -O-C_{1-4} haloalkyl,

(ii) -C_{7-12} fused bicyclic carbocycle in which one ring is a benzene ring and the other ring is saturated or unsaturated, wherein the fused bicyclic carbocycle is optionally substituted with from 1 to 3 substituents each of which is independently halogen, -C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, -O-C_{1-4} haloalkyl,

(iii) aryl selected from phenyl and naphthyl, wherein the aryl is optionally substituted with from 1 to 3 substituents each of which is independently halogen, -C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, -O-C_{1-4} haloalkyl, -CN, -$N(R^aR^b)$, -$C(=O)N(R^aR^b)$, -$C(=O)R^a$, -CO_2R^c, -$S(O)_nR^c$,

$-SO_2N(R^aR^b)$, $-N(R^a)C(=O)R^b$, $-N(R^a)CO_2R^c$, $-N(R^a)SO_2R^c$, $-(CH_2)_{1-2}$-O-C_{1-4} alkyl, $-(CH_2)_{1-2}$-O-C_{1-4} haloalkyl, $-(CH_2)_{1-2}$-CN, $-(CH_2)_{1-2}-N(R^aR^b)$, $-(CH_2)_{1-2}-C(=O)N(R^aR^b)$, $-(CH_2)_{1-2}-C(=O)R^a$, $-(CH_2)_{1-2}-CO_2R^c$, $-(CH_2)_{1-2}-S(O)_nR^c$, $-(CH_2)_{1-2}-SO_2N(R^aR^b)$, $-(CH_2)_{1-2}-N(R^a)C(=O)R^b$, $-(CH_2)_{1-2}-N(R^a)CO_2R^c$, $-(CH_2)_{1-2}-N(R^a)SO_2R^c$, phenyl, $-(CH_2)_{1-2}$-phenyl, HetX, or $-(CH_2)_{1-2}$HetX,

(iv) a 4- to 7-membered saturated heterocyclic ring containing from 1 to 4 heteratoms selected from N, O and S, wherein the saturated heterocyclic ring is optionally substituted with from 1 to 3 substituents each of which is independently halogen, $-C_{1-4}$ alkyl, oxo, phenyl, $-(CH_2)_{1-2}$-phenyl, HetY, or $-(CH_2)_{1-2}$HetY, or

(v) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 3 substituents each of which is independently halogen, $-C_{1-4}$ alkyl, $-O-C_{1-4}$ alkyl, phenyl, $-(CH_2)_{1-2}$-phenyl, HetY, or $-(CH_2)_{1-2}$-HetY;

and all other variables are as defined in the third embodiment;

or a pharmaceutically acceptable salt thereof.

A fourth aspect of the third embodiment of the present invention is a compound of Formula (III), wherein Q^1 is:

(1) -H,
(2) $-C(=O)N(R^aR^b)$,
(3) $-C_{1-6}$ alkyl-$C(=O)N(R^aR^b)$,
(4) -S-C_{1-6} alkyl-$C(=O)N(R^aR^b)$,
(5) -O-C_{1-6} alkyl-$C(=O)N(R^aR^b)$,
(6) $-N(R^a)-C(R^b)=O$,
(7) $-N(SO_2R^c)-C_{1-6}$ alkyl-$C(=O)N(R^aR^b)$,
(8) $-N(R^a)-C(=O)-C(=O)-N(R^aR^b)$,
(9) $-N(R^a)SO_2R^c$,
(10) $-SO_2N(R^aR^b)$,

(11) -CH=CH-C(=O)-N(R^aR^b),
(12) -N(R^a)-C_{1-6} alkyl-C(=O)N(R^aR^b),
(13) -N(R^a)-C(=O)-N(R^aR^b),
(14) -R^k,
(15) -C_{1-6} alkyl-R^k,
(16) -N(R^a)-C_{1-6} alkyl-R^k, or
(17) -C(=O)-R^k;

and all other variables are as originally defined in the third embodiment;

or a pharmaceutically acceptable salt thereof.

A feature of the fourth aspect of the third embodiment is a compound of Formula (III), wherein Q^1 is as defined in the fourth aspect, except that R^k in the definition of Q^1 is:

(i) a 4- to 7-membered saturated heterocyclic ring containing from 1 to 4 heteratoms independently selected from N, O and S, wherein the saturated heterocyclic ring is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-4} alkyl, -C_{3-6} cycloalkyl, -O-C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} haloalkyl, -CN, oxo, phenyl, benzyl, phenylethyl, -$(CH_2)_{0-3}$C(=O)N(R^aR^b), -$(CH_2)_{0-3}$C(=O)R^a, - N(R^a)-C(=O)R^b, -N(R^a)-CO_2R^c, -$(CH_2)_{1-3}$N(R^a)-C(=O)R^b, -N(R^aR^b), -$(CH_2)_{1-3}$N(R^aR^b), -SO_2R^c, -$(CH_2)_{0-3}$C(=O)-HetY, -HetY, -N(R^a)-HetY, and -$(CH_2)_{1-3}$-HetY; wherein each HetY is independently a 5- or 6-membered heteroaromatic ring containing from 1 to 4 nitrogen atoms or a 5- or 6-membered saturated heterocyclic ring containing from 1 to 4 nitrogen atoms, wherein the ring is optionally substituted with 1 or 2 substituents each of which is independently halogen, oxo, -C_{1-4} alkyl, or -O-C_{1-4} alkyl; or

(ii) a 7- to 9-membered bridged azabicycloalkyl saturated ring system containing a C_{5-7} azacycloalkyl ring in which two of the ring carbons are connected by a bridge containing 1 or 2 carbon atoms; wherein the bridged azabicycloalkyl ring system is optionally substituted with from 1 to 4 substituents each of which is independently halogen, oxo, or -C_{1-4} alkyl;

and all other variables are as originally defined in the third embodiment;

or a pharmaceutically acceptable salt thereof.

Another feature of the fourth aspect of the third embodiment is a compound of Formula (III), or a pharmaceutically acceptable salt thereof, wherein Q^1 is as defined in the fourth aspect, except that R^k in the definition of Q^1 is restricted to a 4- to 7-membered saturated heterocyclic ring as defined in (i) of the preceding feature.

A fifth aspect of the third embodiment of the present invention is a compound of Formula (III), wherein Q^1 is:

(1) $-C(=O)N(R^aR^b)$,
(2) $-CH_2-C(=O)N(R^aR^b)$,
(3) $-CH_2CH_2-C(=O)N(R^aR^b)$,
(4) $-S-CH_2-C(=O)N(R^aR^b)$,
(5) $-O-CH_2-C(=O)N(R^aR^b)$,
(6) $-N(R^a)-C(R^b)=O$,
(7) $-N(SO_2R^c)-CH_2-C(=O)N(R^aR^b)$,
(8) $-N(R^a)-C(=O)-C(=O)-N(R^aR^b)$,
(9) $-N(R^a)SO_2R^c$,
(10) $-CH=CH-C(=O)-N(R^aR^b)$,
(11) $-N(R^a)-CH_2-C(=O)N(R^aR^b)$,
(12) $-N(R^a)-C(=O)-N(R^aR^b)$,
(13) $-R^k$,
(14) $-(CH_2)_{1-3}$ alkyl-R^k, or
(15) $-N(R^a)-(CH_2)_{1-3}-R^k$;

and all other variables are as originally defined in the third embodiment;

or a pharmaceutically acceptable salt thereof.

A feature of the fifth aspect of the third embodiment is a compound of Formula (III), wherein Q^1 is as defined in the fifth aspect, except that R^k in the definition of Q^1 is:

(i) a saturated heterocyclic ring selected from piperidinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, isothiazolidinyl, oxazolidinyl, isooxazolidinyl, pyrrolidinyl, imidazolidinyl, piperazinyl, tetrahydrofuranyl, pyrazolidinyl, hexahydropyrimidinyl, thiazinanyl, thiazepanyl, thiadiazepanyl, dithiazepanyl, diazepanyl, and thiadiazinanyl, wherein the saturated heterocyclic ring is unsubstituted or substituted with 1 to 4 substituents each of which is independently:

(a) methyl or ethyl,
(b) =O,
(c) $-C(=O)N(R^aR^b)$,
(d) $-CH_2C(=O)N(R^aR^b)$,
(e) $-C(=O)R^a$, or
(f) $-SO_2R^c$; or

(ii) a bridged azabicycloalkyl selected from azabicyclo[2.2.1]cycloheptyl and azabicyclo[2.2.2]cyclooctyl, wherein the azabicycloalkyl is optionally substituted with 1 or 2 substituents each of which is independently halogen or C_{1-4} alkyl;

and all other variables are as originally defined in the third embodiment;

or a pharmaceutically acceptable salt thereof.

Another feature of the fifth aspect of the third embodiment is a compound of Formula (III), or a pharmaceutically acceptable salt thereof, wherein Q^1 is as defined in the fifth aspect, except that R^k in the definition of Q^1 is restricted to a 4- to 7-membered saturated heterocyclic ring as defined in (i) of the preceding feature.

In a sub-feature of either of the two preceding features of the fifth aspect, each R^a is independently -H, $-C_{1-4}$ alkyl, or cyclopropyl; each R^b is independently -H, $-C_{1-4}$ alkyl, or cyclopropyl; and each R^c is independently a $-C_{1-4}$ alkyl or cyclopropyl.

A sixth aspect of the third embodiment of the present invention is a compound of Formula (III), wherein Q^1 is $-C(=O)N(R^aR^b)$, $-N(R^a)SO_2R^c$, $-N(R^a)-C(=O)-C(=O)-N(R^aR^b)$, 1,1-dioxido-1,2-thiazinan-2-yl, 1,1-dioxidoisothiazolidin-2-yl, 1,1-dioxido-1,2,6-thiadiazinan-2-yl, 6-methyl-1,1-

dioxido-1,2,6-thiadiazinan-2-yl, or 3-oxo-2-azabicyclo[2.2.1]hept-2-yl; and all other variables are as originally defined in the third embodiment; or a pharmaceutically acceptable salt thereof.

A seventh aspect of the third embodiment of the present invention is a compound of Formula (III), wherein Q^1 is $-C(=O)N(R^aR^b)$, $-N(R^a)SO_2R^c$, or 1,1-dioxido-1,2-thiazinan-2-yl; and all other variables are as originally defined in the third embodiment; or a pharmaceutically acceptable salt thereof.

An eighth aspect of the third embodiment of the present invention is a compound of Formula (III), wherein each of Q^2 and Q^3 are both -H; and all other variables are as originally defined in the third embodiment; or a pharmaceutically acceptable salt thereof.

A ninth aspect of the third embodiment of the present invention is a compound of Formula (III), wherein R^{1a}, R^{1b}, and R^{1c} are each independently -H, fluoro, chloro, bromo, $-C_{1-4}$ alkyl, or $-CF_3$; and all other variables are as originally defined in the third embodiment; or a pharmaceutically acceptable salt thereof.

A tenth aspect of the third embodiment of the present invention is a compound of Formula (III), wherein R^{1b} and R^{1c} are both -H; and R^{1a} is -H, halogen, $-C_{1-6}$ alkyl, or $-C_{1-6}$ haloalkyl; and all other variables are as originally defined in the third embodiment; or a pharmaceutically acceptable salt thereof.

In a feature of the tenth aspect of the third embodiment, R^{1b} and R^{1c} are both -H; and R^{1a} is -H, fluoro, chloro, bromo, $-C_{1-4}$ alkyl, or $-CF_3$. In another feature of the tenth aspect, R^{1b} and R^{1c} are both -H; and R^{1a} is -H or fluoro. In still another feature of the tenth aspect, R^{1b} and R^{1c} are both -H; and R^{1a} is fluoro.

An eleventh aspect of the third embodiment is a compound of Formula (III), wherein Z is -H; and all other variables are as originally defined in the third embodiment; or a pharmaceutically acceptable salt thereof.

A twelfth aspect of the third embodiment is a compound of Formula (III), wherein each R^a is independently -H, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, or cyclopropyl; each R^b is independently -H, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, or cyclopropyl; and each R^c is independently a $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, or cyclopropyl; and all other variables are as originally defined in the third embodiment; or a pharmaceutically acceptable salt thereof.

A feature of the twelfth aspect of the third embodiment is a compound of Formula (III), wherein each R^a is independently -H, methyl, ethyl, $-CF_3$, or cyclopropyl; each R^b is independently -H, methyl, ethyl, $-CF_3$, or cyclopropyl; and

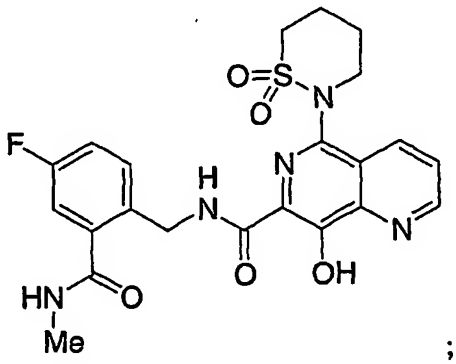
each R^c is independently methyl, ethyl, $-CF_3$, or cyclopropyl; and all other variables are as originally defined in the third embodiment; or a pharmaceutically acceptable salt thereof.

Another feature of the twelfth aspect is a compound of Formula (III), wherein each R^a is independently -H, methyl, or ethyl; each R^b is independently -H, methyl, or ethyl; and each R^c is independently methyl or ethyl; and all other variables are as originally defined in the third embodiment; or a pharmaceutically acceptable salt thereof.

Additional aspects of the third embodiment of the present invention include, but are not limited to, compounds of Formula (III) wherein each of two or three or more of R^{1a}, R^{1b}, R^{1c}, R^{2a}, R^{2b}, Q^1, Q^2, Q^3, Z, R^a, R^b, R^c, and R^k is independently defined in accordance with its definition in one of the aspects, or a feature or sub-feature thereof, as set forth above. Any and all possible combinations of these variables in Formula (III) are additional aspects of the third embodiment of the present invention.

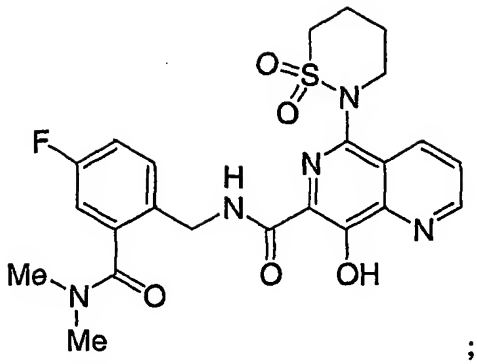
Another embodiment of the present invention is a compound selected from the group consisting of

N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide (also referred to herein as Compound A):



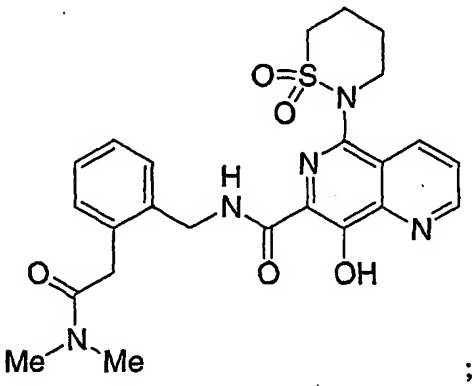
;

N-{2-[(dimethylamino)carbonyl]-4-fluorobenzyl}-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide:



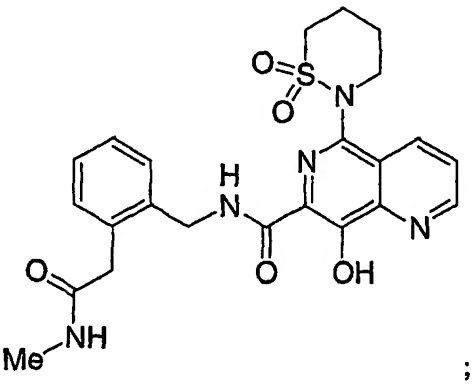
;

N-{2-[2-(dimethylamino)-2-oxoethyl]benzyl}-5- (1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide:



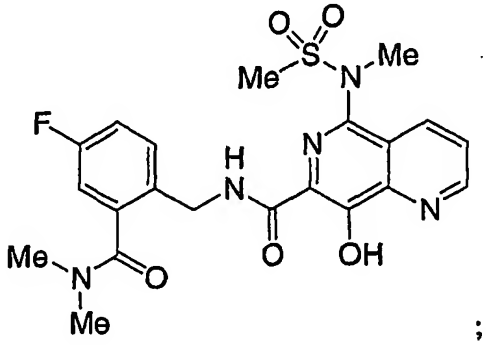
;

N-{2-[2-(methylamino)-2-oxoethyl]benzyl}-5-(1,1-Dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide:



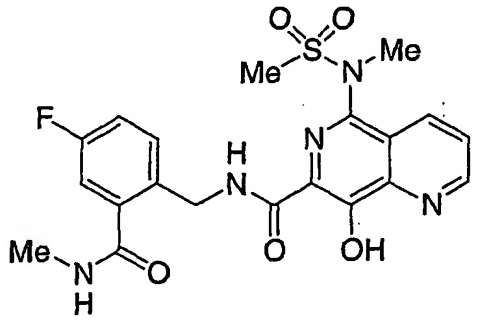
;

N-{2-[(dimethylamino)carbonyl]-4-fluorobenzyl}-5-[methyl(methylsulfonyl)amino]-8-hydroxy-1,6-naphthyridine-7-carboxamide:



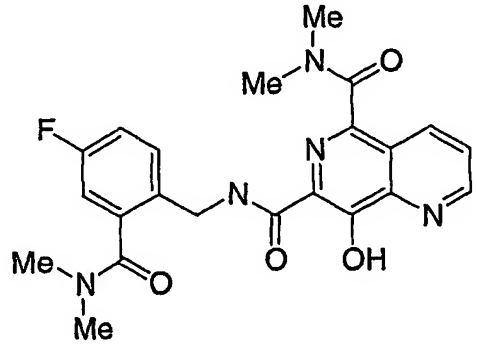
;

N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-5-[methyl(methylsulfonyl)amino]-8-hydroxy-1,6-naphthyridine-7-carboxamide:



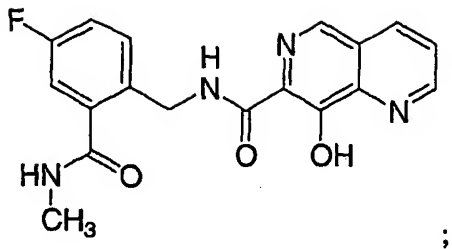
;

N-{2-[(dimethylamino)carbonyl]-4-fluorobenzyl}-5-[(dimethylamino)carbonyl]-8-hydroxy-1,6-naphthyridine-7-carboxamide:



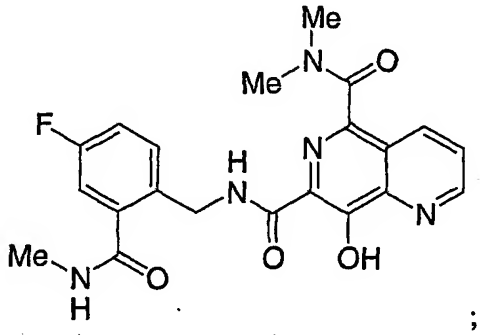
;

N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-8-hydroxy-1,6-naphthyridine-7-carboxamide:



;

N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-5-[(dimethylamino)carbonyl]-8-hydroxy-1,6-naphthyridine-7-carboxamide:



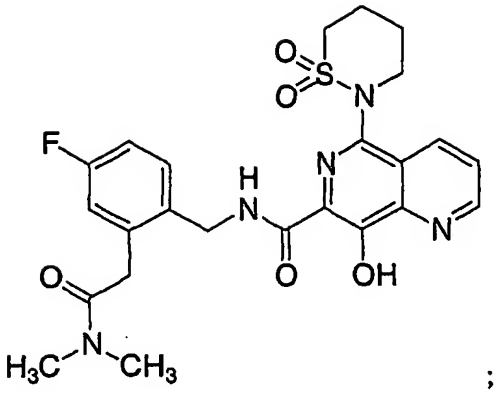
;

and pharmaceutically acceptable salts thereof.

An aspect of the preceding embodiment of the present invention is Compound A or a pharmaceutically acceptable salt thereof (e.g., a potassium salt or a sodium salt). Compound A has exhibited improved antiviral properties relative to the closely related N-benzyl-8-hydroxy-1,6-naphthyridine carboxamide integrase inhibitors not having an ortho polar substituent on the phenyl ring of the N-benzyl amide. These properties include improved antiviral potency in the presence of human serum proteins, and also retention of significant antiviral activity against several HIV mutants that are resistant to other integrase inhibitors.

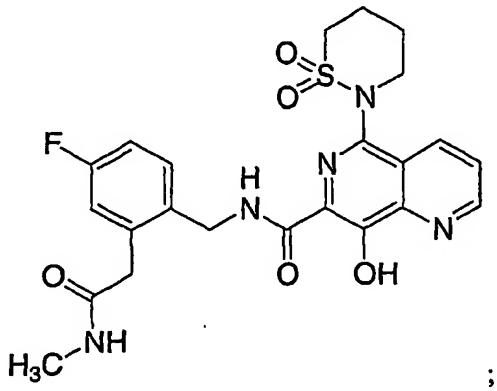
Still another embodiment of the present invention is a compound selected from the group consisting of:

N-{2-[2-(dimethylamino)-2-oxoethyl]-4-fluorobenzyl}-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide:



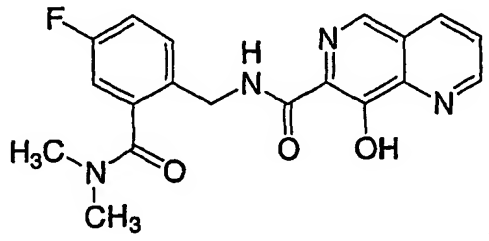
;

5-(1,1-dioxido-1,2-thiazinan-2-yl)-N-{4-fluoro-2-[2-(methylamino)-2-oxoethyl]benzyl}-8-hydroxy-1,6-naphthyridine-7-carboxamide:



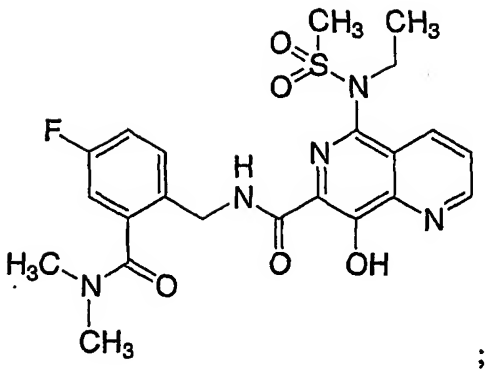
;

N-{2-[(dimethylamino)carbonyl]-4-fluorobenzyl}-8-hydroxy-1,6-naphthyridine-7-carboxamide:



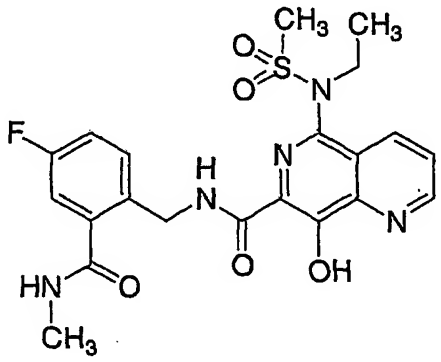
;

N-{2-[(dimethylamino)carbonyl]-4-fluorobenzyl}-5-[ethyl(methylsulfonyl)amino]-8-hydroxy-1,6-naphthyridine-7-carboxamide:



;

5-[ethyl(methylsulfonyl)amino]-N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-8-hydroxy-1,6-naphthyridine-7-carboxamide:



;

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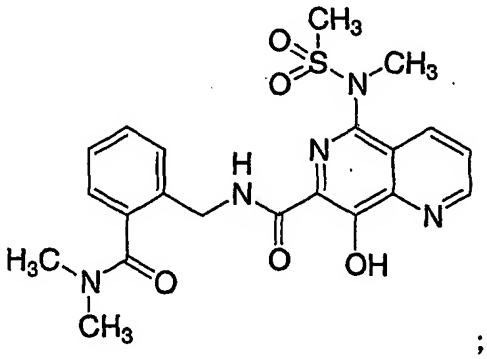
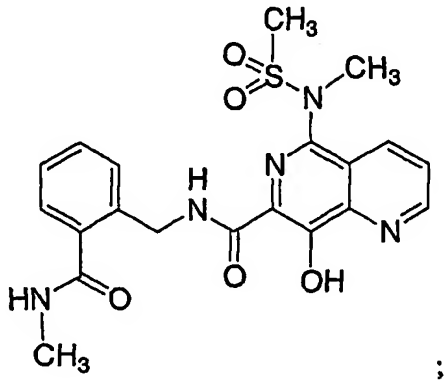
N-{2-[(dimethylamino)carbonyl]benzyl}-8-hydroxy-5-[methyl(methylsulfonyl)amino]-1,6-naphthyridine-7-carboxamide:



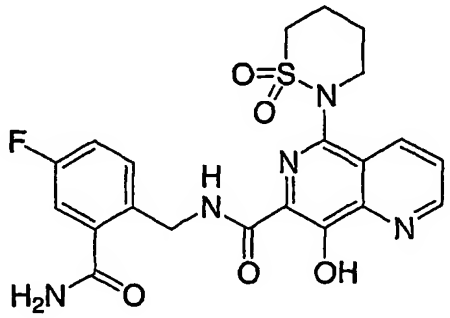
;

8-hydroxy-N-{2-[(methylamino)carbonyl]benzyl}-5-[methyl(methylsulfonyl)amino]-1,6-naphthyridine-7-carboxamide:



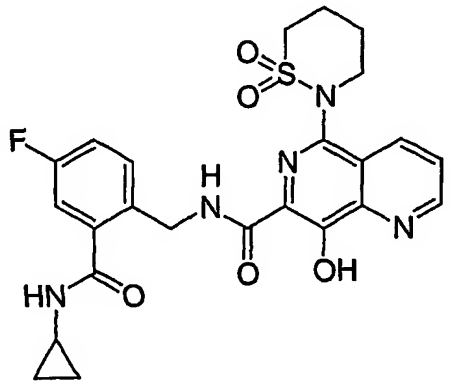
;

N-[2-(aminocarbonyl)-4-fluorobenzyl]-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide:



;

N-{2-[(cyclopropylamino)carbonyl]-4-fluorobenzyl}-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide:



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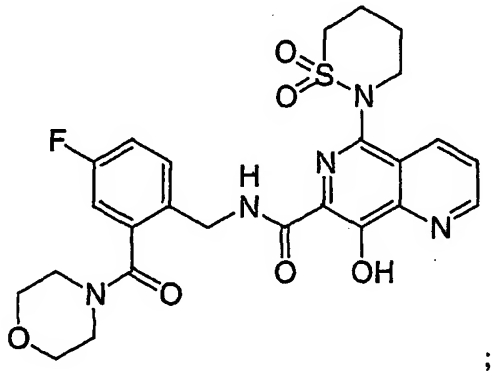
5-(1,1-dioxido-1,2-thiazinan-2-yl)-N-[4-fluoro-2-(morpholin-4-ylcarbonyl)benzyl]-8-hydroxy-1,6-naphthyridine-7-carboxamide:



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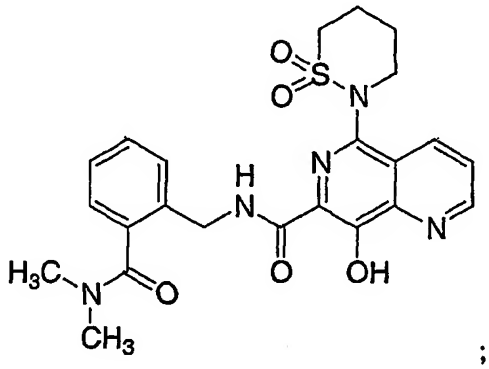
N-{2-[(dimethylamino)carbonyl]benzyl}-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide:



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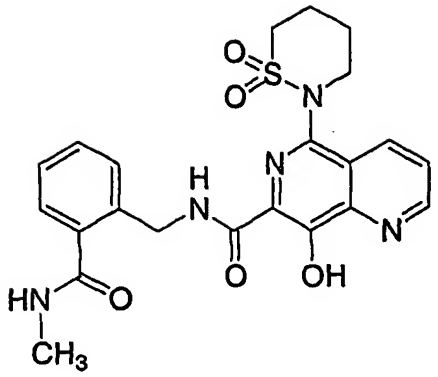
5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-N-{2-[(methylamino)carbonyl]benzyl}-1,6-naphthyridine-7-carboxamide:



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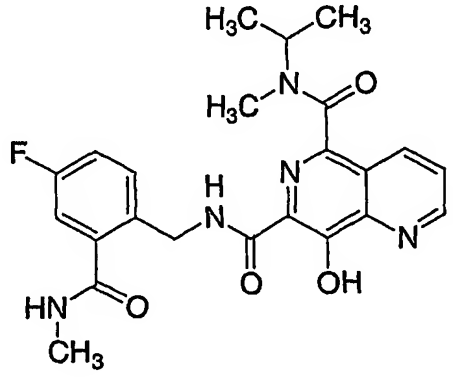
N-7-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-8-hydroxy-N-5-isopropyl-N-5-methyl-1,6-naphthyridine-5,7-dicarboxamide:



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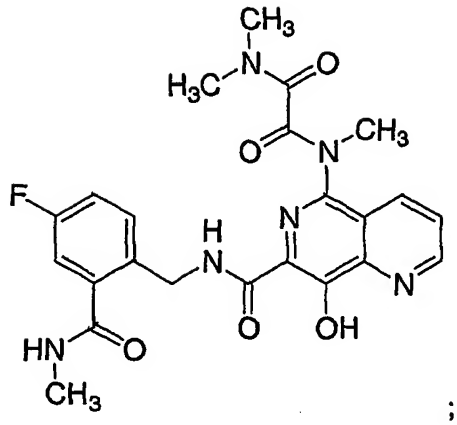
N-1-{7-[({4-fluoro-2-[(methylamino)carbonyl]benzyl}amino)carbonyl]-8-hydroxy-1,6-naphthyridin-5-yl}-N-1-,N-2,N-2-trimethylethanediamide:



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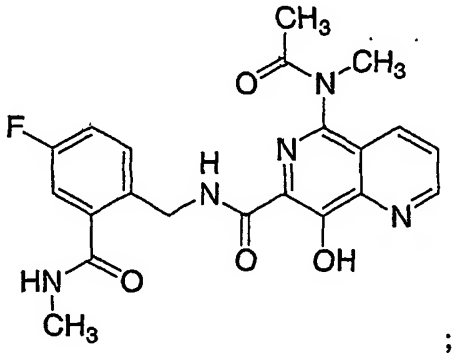
5-[acetyl(methyl)amino]-N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-8-hydroxy-1,6-naphthyridine-7-carboxamide:



;

and pharmaceutically acceptable salts thereof.

Still another embodiment of the present invention is a compound selected from the group consisting of:

N-{4-fluoro-2-[(isopropylamino)carbonyl]benzyl}-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{4-fluoro-2-[(ethylamino)carbonyl]benzyl}-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{4-fluoro-2-[(n-propylamino)carbonyl]benzyl}-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{4-fluoro-2-[(amino)carbonyl]benzyl}-5-[methyl(methylsulfonyl)amino]-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{4-fluoro-2-[(ethylamino)carbonyl]benzyl}-5-[methyl(methylsulfonyl)amino]-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-[2-(1H-1,2,4-triazol-1-yl)benzyl]-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-[2-(1H-1,2,4-tetrazol-1-yl)benzyl]-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-8-hydroxy-5-[(1R,4S)-3-oxo-2-azabicyclo[2.2.1]hept-2-yl]-1,6-naphthyridine-7-carboxamide;

N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-8-hydroxy-5-[(1S,4R)-3-oxo-2-azabicyclo[2.2.1]hept-2-yl]-1,6-naphthyridine-7-carboxamide;

N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-5-[(ethylsulfonyl)(methyl)amino]-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{4-fluoro-2-[(dimethylamino)carbonyl]benzyl}-5-[(ethylsulfonyl)(methyl)amino]-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-5-(1,1-dioxidoisothiazolidin-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-5-(6-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{4-fluoro-2-[(dimethylamino)carbonyl]benzyl}-5-(6-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-[2-(acetylamino)-4-fluorobenzyl]-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

5-(1,1-dioxido-1,2-thiazinan-2-yl)-N-[4-fluoro-2-(2-oxopyrrolidin-1-yl)benzyl]-8-hydroxy-1,6-naphthyridine-7-carboxamide

and pharmaceutically acceptable salts thereof.

Other embodiments of the present invention include the following:

(a) A pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention (e.g., a compound of Formula (I) or Formula (II) or Formula (III) or any of the specific compounds set forth above) and a pharmaceutically acceptable carrier.

(b) A pharmaceutical composition which comprises the product prepared by combining (e.g., mixing) a therapeutically effective amount of a compound of the invention and a pharmaceutically acceptable carrier.

(c) The pharmaceutical composition of (a) or (b), further comprising a therapeutically effective amount of an HIV infection/AIDS treatment agent selected from the group consisting of HIV/AIDS antiviral agents, immunomodulators, and anti-infective agents.

(d) The pharmaceutical composition of (c), wherein the HIV infection/AIDS treatment agent is an antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, and nucleoside HIV reverse transcriptase inhibitors.

(e) A combination useful for inhibiting HIV integrase, for treating or preventing infection by HIV, or for preventing, treating or delaying the onset of AIDS, which is a therapeutically effective amount of a compound of the invention and a therapeutically effective amount of an HIV infection/AIDS treatment agent selected from the group consisting of HIV/AIDS antiviral agents, immunomodulators, and anti-infective agents.

(f) The combination of (e), wherein the HIV infection/AIDS treatment agent is an antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors and nucleoside HIV reverse transcriptase inhibitors.

(g) A method of inhibiting HIV integrase in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of a compound of the invention.

(h) A method of preventing or treating infection by HIV in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of a compound of the invention.

(i) The method of (h), wherein the compound of the invention is administered in combination with a therapeutically effective amount of at least one antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, and nucleoside HIV reverse transcriptase inhibitors.

(j) A method of preventing, treating or delaying the onset of AIDS in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of a compound of the invention.

(k) The method of (j), wherein the compound is administered in combination with a therapeutically effective amount of at least one antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, and nucleoside HIV reverse transcriptase inhibitors

(l) A method of inhibiting HIV integrase in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), (c) or (d) or the combination of (e) or (f).

(m) A method of preventing or treating infection by HIV in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), (c) or (d) or the combination of (e) or (f).

(n) A method of preventing, treating or delaying the onset of AIDS in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), (c) or (d) or the combination of (e) or (f).

The present invention also includes a compound of the present invention (i) for use in, (ii) for use as a medicament for, or (iii) for use in the preparation of a medicament for: (a) inhibiting HIV protease, (b) preventing or treating infection by HIV, or (c) preventing, treating or delaying the onset of AIDS. In these uses, the compounds of the present invention can optionally be employed in combination with one or more HIV/AIDS treatment agents selected from HIV/AIDS antiviral agents, anti-infective agents, and immunomodulators.

Additional embodiments of the invention include the pharmaceutical compositions, combinations and methods set forth in (a)-(n) above and the uses set forth in the preceding paragraph, wherein the compound of the present invention employed therein is a compound of one of the embodiments, or an aspect or feature or sub-feature thereof, described above. In all of these embodiments, the compound may optionally be used in the form of a pharmaceutically acceptable salt.

As used herein, the term "C_{1-6} alkyl" (or "C_1-C_6 alkyl") means linear or branched chain alkyl groups having from 1 to 6 carbon atoms and includes all of the hexyl alkyl and pentyl alkyl isomers as well as n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl. "C_{1-4} alkyl" means n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl.

The term "-C_{1-6} alkyl-" refers to a C_1 to C_6 linear or branched alkyl group as just defined which is bivalent. It can alternatively be referred to as "C_{1-6} alkylene" or "C_{1-6} alkanediyl". A class of alkylenes of particular interest with respect to the invention is -$(CH_2)_{1-6}$-, and sub-classes of particular interest include -$(CH_2)_{1-4}$-, -$(CH_2)_{1-3}$-, -$(CH_2)_{1-2}$-, and -CH_2-.

The term "C_{2-6} alkenyl" (or "C_2-C_6 alkenyl") means linear or branched chain alkenyl groups having from 2 to 6 carbon atoms and includes all of the hexenyl and pentenyl isomers as well as 1-butenyl, 2-butenyl, 3-butenyl, isobutenyl, 1-propenyl, 2-propenyl, and ethenyl (or vinyl). Similar terms such as "C_{2-4} alkenyl" have an analogous meaning. A class of alkenyls of particular interest with respect to the invention is -CH_2=CH-$(CH_2)_{1-4}$H, and sub-classes of particular interest include -CH=CH-$(CH_2)_{1-2}$H, -CH=CH-CH_3, and-CH=CH_2. Another class of alkenyls of particular interest with respect to the invention is -$(CH_2)_{1-2}$-CH=CH-$(CH_2)_{1-2}$H.

The term "C_{2-5} alkynyl" (or "C_2-C_5 alkynyl") means linear or branched chain alkynyl groups having from 2 to 5 carbon atoms and includes all of the pentynyl isomers as well as 1-butynyl, 2-butynyl, 3-butynyl, 1-propynyl, 2-propynyl, and ethynyl (or acetylenyl). Similar terms such as "C_{2-4} alkynyl" have an analogous meaning. A class of alkynyls of particular interest with respect to the invention is $-C\equiv C-(CH_2)_{1-4}H$ (e.g., $-C\equiv C-CH_3$).

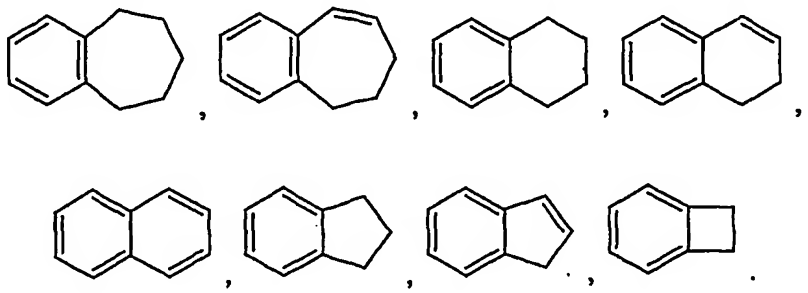
The term "C_{3-8} cycloalkyl" (or "C_3-C_8 cycloalkyl") means a cyclic ring of an alkane having three to eight total carbon atoms (i.e., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl). Similar terms such as "C_{3-6} cycloalkyl" have an analogous meaning.

The term "halogen" (or "halo") refers to fluorine, chlorine, bromine and iodine (alternatively referred to as fluoro, chloro, bromo, and iodo).

The term "C_{1-6} haloalkyl" (which may alternatively be referred to as "C_1-C_6 haloalkyl" or "halogenated C_1-C_6 alkyl") means a C_1 to C_6 linear or branched alkyl group as defined above with one or more halogen substituents. The term "C_{1-4} haloalkyl" has an analogous meaning. The term "C_{1-6} fluoroalkyl" has an analogous meaning except that the halogen substituents are restricted to fluoro. A class of fluoroalkyls of particular interest with respect to the invention is the series $(CH_2)_{0-4}CF_3$ (i.e., trifluoromethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoro-n-propyl, etc.).

The term "carbocycle" (and variations thereof such as "carbocyclic" or "carbocyclyl") as used herein refers to (i) a C_3 to C_8 monocyclic, saturated or unsaturated ring, (ii) a C_7 to C_{12} bicyclic ring system, or (iii) a C_{11} to C_{16} tricyclic ring system, wherein each ring in (ii) or (iii) is independent of, bridged with, or fused to the other ring or rings and each ring is saturated or unsaturated. The carbocycle may be attached to the rest of the molecule at any carbon atom which results in a stable compound. When the carbocyclic ring has substituents, it is understood that the substituents may be attached to any atom in the ring that results in a stable chemical structure.

The fused bicyclic carbocycles are a subset of the carbocycles; i.e., the term "fused bicyclic carbocycle" generally refers to a C_7 to C_{12} bicyclic ring system in which each ring is saturated or unsaturated and two adjacent carbon atoms are shared by each of the rings in the ring system. Fused tricyclic carbocycles have an analogous meaning. A subset of the fused bicyclic carbocycles are those bicyclic carbocycles in which one ring is a benzene ring and the other ring is saturated or unsaturated, with attachment via any carbon atom that results in a stable compound. Representative examples of this subset include the following:



Aryl groups form a subset of the carbocycles; i.e., the term "aryl" as used herein refers to an aromatic carbocyclic ring or an aromatic carbocyclic fused ring system. The fused ring system contains two or more carbocyclic rings in which each ring shares two adjacent carbon atoms with at least one other ring. The aryl group may be attached to the rest of the molecule at any carbon atom which results in a stable compound.

A subset of aryl groups particularly suitable for use in the present invention (e.g., in the definition of R^k) includes those selected from phenyl, naphthyl, anthryl, and phenanthryl. Another particularly suitable subset of aryl groups is phenyl and naphthyl. Still another particularly suitable subset of aryl groups is phenyl per se.

A subset of carbocycles particularly suitable for use in the present invention (e.g., in the definition of R^k) includes any carbocycle which is (i) -C_{3-8} cycloalkyl or (ii) aryl. Another particularly suitable subset includes any carbocycle which is -C_{3-8} cycloalkyl, phenyl, naphthyl, anthryl, or phenanthryl. Still another particularly suitable subset includes any carbocycle which is -C_{3-8} cycloalkyl, phenyl, or naphthyl. Yet another particularly suitable subset is phenyl and naphthyl, and still another is phenyl per se.

The term "heterocycle" (and variations thereof such as "heterocyclic" or "heterocyclyl") refers to (i) a 4- to 8-membered, saturated or unsaturated monocyclic ring, (ii) a 7- to 12-membered bicyclic ring system, or (iii) an 11 to 16-membered tricyclic ring system; wherein each ring in (ii) or (iii) is independent of, bridged with, or fused to the other ring or rings and each ring is saturated or unsaturated, and the monocyclic ring, bicyclic ring system, or tricyclic ring system contains one or more heteroatoms (e.g., from 1 to 6 heteroatoms, from 1 to 5 heteroatoms, or from 1 to 4 heteroatoms) independently selected from N, O and S and a balance of carbon atoms (the monocylic ring typically contains at least one carbon atom and the ring systems typically contain at least two carbon atoms); and wherein any one or more of the nitrogen and sulfur heteroatoms is optionally oxidized, and any one or more of the nitrogen heteroatoms is optionally quaternized. The heterocyclic ring may be attached to the rest of the molecule via any heteroatom or carbon atom in the ring, provided that attachment results in the creation of a stable structure. When the heterocyclic ring has substituents, it is understood that the substituents may be attached to any atom in the ring, whether a heteroatom or a carbon atom, provided that a stable chemical structure results.

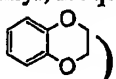
Heterocycles as defined in the preceding paragraph but excluding bicyclic and tricyclic ring systems containing a ring that is bridged with another ring form a subset of heterocycles of interest herein.

Saturated heterocyclics form a subset of the heterocycles; i.e., the term "saturated heterocyclic" generally refers to a heterocycle as defined above in which the entire ring system (whether mono- or poly-cyclic) is saturated. The term "saturated heterocyclic ring" refers to a 4- to 7-membered saturated monocyclic ring which consists of carbon atoms and one or more heteroatoms (e.g., from 1 to 4, or from 1 to 3, or from 1 to 2 heteroatoms; or 1 heteroatom) independently selected from N, O and S. Representative examples include piperidinyl, piperazinyl, azepanyl (i.e., ), pyrrolidinyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, morpholinyl (alternatively referred to as morpholino), thiomorpholinyl (or thiomorpholino), thiazolidinyl, isothiazolidinyl, tetrahydrothienyl, tetrahydrofuryl (or tetrahydrofuranyl), thiazinanyl (e.g., 1,2-thiazinanyl ), thiadiazinanyl (e.g., 1,2,6-thiadiazinanyl ), and dioxanyl.

Bridged bicyclic saturated heterocycles from another subset of the heterocycles; i.e. the term generally refers to a bicyclic heterocycle as defined above in which the entire ring system is saturated and the two rings are formed by a bridge connecting two atoms in the same ring, wherein the bridge contains at least one atom which is C, N, O, or S. Of particular interest herein are the 7- to 9-membered bridged azabicycloalkyl saturated ring systems containing a C_{5-7} azacycloalkyl ring wherein two of its ring carbons are connected by a bridge containing 1 or 2 carbon atoms. The bridged azabicycloalkyl ring systems include azabicyclo[2.1.1]hexyl, azabicyclo[2.2.1]heptyl (e.g., 2-azabicyclo[2.2.1]hept-2-yl), and azabicyclo[2.2.2]octyl.

Heteroaromatics form another subset of the heterocycles; i.e., the term "heteroaromatic" (alternatively "heteroaryl") generally refers to a heterocycle as defined above in which the entire ring system (whether mono- or poly-cyclic) is an aromatic ring system. The term "heteroaromatic ring" refers a 5- or 6-membered monocyclic aromatic ring which consists of carbon atoms and one or more heteroatoms (e.g., from 1 to 4, or from 1 to 3, or from 1 to 2 heteroatoms; or 1 heteroatom) independently selected from N, O and S. Representative examples of

heteroaromatic rings include pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl (or thiophenyl), thiazolyl, furanyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isooxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, and thiadiazolyl.

Representative examples of bicyclic heterocycles include benzotriazolyl, indolyl, isoindolyl, indazolyl, indolinyl, isoindolinyl, quinoxalinyl, quinazolinyl, cinnolinyl, chromanyl, isochromanyl, tetrahydroquinolinyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzo-1,4-dioxinyl (i.e., ), and benzo-1,3-dioxolyl (i.e., ).

Representative examples of tricyclic heterocycles include phenothiazinyl, carbazolyl, beta-carbolinyl, tetrahydro-beta-carbolinyl, acridinyl, phenazinyl, and phenoxazinyl.

A subset of heterocycles particularly suitable for use in the present invention (e.g., in the definition of R^k) includes any heterocycle which is (i) a 4- to 7-membered saturated heterocyclic ring containing from 1 to 4 heteratoms selected from N, O and S, or (ii) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S. Another particularly suitable subset includes any heterocycle which is (i) a 5 or 6-membered saturated heterocyclic ring containing from 1 to 4 heteratoms independently selected from N, O and S, or (ii) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S. Still another particularly suitable subset includes any heterocycle which is (i) a 5 or 6-membered saturated heterocyclic ring containing from 1 to 3 heteratoms independently selected from N, O and S, or (ii) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S.

A subset of heteroaryl groups particularly suitable for use in the present invention (e.g., in the definition of R^k) includes any heteroaryl which is a 5- or 6-membered heteraromatic ring containing from 1 to 4 heteroatoms or a 9- or 10-membered bicyclic heteroaromatic ring system containing from 1 to 6 heteroatoms, wherein the heteroatoms in the heteroaryl are independently selected from N, O and S. Another particularly suitable subset of aryl groups includes any heteroaryl which is a 5- or 6-membered heteraromatic ring containing from 1 to 4 heteroatoms. Still another particularly suitable subset of heteroaryl groups includes any heteroaryl which is pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, furanyl, imidazolyl,

pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isooxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, or thiadiazolyl.

Unless expressly stated to the contrary, an "unsaturated" ring is a partially or fully unsaturated ring. For example, an "unsaturated monocyclic C_6 carbocycle" refers to cyclohexene, cyclohexadiene, and benzene.

Unless expressly stated to the contrary, all ranges cited herein are inclusive. For example, a heterocycle described as containing from "1 to 4 heteroatoms" means the heterocycle can contain 1, 2, 3 or 4 heteroatoms.

When any variable (e.g., R^a, R^b, or R^c) occurs more than one time in any constituent or in Formula I or in any other formula depicting and describing compounds of the invention, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

The term "substituted" (e.g., as in "aryl which is optionally substituted with from 1 to 5 substituents ...") includes mono- and poly-substitution by a named substituent to the extent such single and multiple substitution (including multiple substitution at the same site) is chemically allowed.

The symbol " ~~~ " in front of an open bond in the structural formula of a group marks the point of attachment of the group to the rest of the molecule.

The compounds of the present invention may have asymmetric centers and may occur, except when specifically noted, as mixtures of stereoisomers or as individual diastereomers, or enantiomers, with all isomeric forms being included in the present invention.

The compounds of the present invention are useful in the inhibition of HIV integrase, the prevention or treatment of infection by human immunodeficiency virus (HIV) and the prevention, treatment or the delay in the onset of consequent pathological conditions such as AIDS. Preventing AIDS, treating AIDS, delaying the onset of AIDS, or preventing or treating infection by HIV is defined as including, but not limited to, treatment of a wide range of states of HIV infection: AIDS, ARC (AIDS related complex), both symptomatic and asymptomatic, and actual or potential exposure to HIV. For example, the compounds of this invention are useful in treating infection by HIV after suspected past exposure to HIV by such means as blood transfusion, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery.

The compounds of this invention are useful in the preparation and execution of screening assays for antiviral compounds. For example, the compounds of this invention are useful for isolating enzyme mutants, which are excellent screening tools for more powerful antiviral compounds. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other antivirals to HIV integrase, e.g., by competitive inhibition. Thus the compounds of this invention are commercial products to be sold for these purposes.

The compounds of the present invention can be administered in the form of pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt" refers to a salt which possesses the effectiveness of the parent compound and which is not biologically or otherwise undesirable (e.g., is neither toxic nor otherwise deleterious to the recipient thereof). Suitable salts include acid addition salts which may, for example, be formed by mixing a solution of the compound of the present invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, acetic acid, trifluoroacetic acid, or benzoic acid. When the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof can include alkali metal salts (e.g., sodium or potassium salts), alkaline earth metal salts (e.g., calcium or magnesium salts), and salts formed with suitable organic ligands such as quaternary ammonium salts. Also, in the case of an acid (-COOH) or alcohol group being present, pharmaceutically acceptable esters can be employed to modify the solubility or hydrolysis characteristics of the compound.

For the purpose of preventing or treating HIV infection or preventing, treating or delaying the onset of AIDS, the compounds of the present invention can be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in the form of a unit dosage of a pharmaceutical composition containing a therapeutically effective amount of the compound and conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention mean providing the compound to the individual in need of treatment. When a compound of the invention is provided in combination with one or more other active agents (e.g., antiviral agents useful for treating HIV infection or AIDS), "administration" and its variants are each understood to include concurrent and sequential provision of the compound and other agents.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combining the specified ingredients in the specified amounts.

By "pharmaceutically acceptable" is meant that the ingredients of the pharmaceutical composition must be compatible with each other and not deleterious to the recipient thereof.

The term "subject" (which may be alternatively referred to herein as "patient") as used herein refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease being treated. The term also includes a prophylactically effective amount suitable for prevention of the disease or condition. When the active compound (i.e., active ingredient) is administered as the salt, references to the amount of active ingredient are to the free acid or free base form of the compound.

The pharmaceutical compositions can be in the form of orally-administrable suspensions or tablets or capsules, nasal sprays, sterile injectible preparations, for example, as sterile injectible aqueous or oleagenous suspensions or suppositories. These compositions can be prepared by methods and contain excipients which are well known in the art. Suitable methods and ingredients are described in Remington's Pharmaceutical Sciences, 18th edition, edited by A. R. Gennaro, Mack Publishing Co., 1990, which is herein incorporated by reference in its entirety. In one embodiment, the pharmaceutical composition is a capsule or a tablet suitable for oral administration comprising a compound of the present invention (e.g., Compound A or a salt thereof) and a nonionic surfactant (e.g., a poloxamer).

The compounds of this invention can be administered orally in a dosage range of 0.001 to 1000 mg/kg of mammal (e.g., human) body weight per day in a single dose or in divided doses. One preferred dosage range is 0.01 to 500 mg/kg body weight per day orally in a single dose or in divided doses. Another preferred dosage range is 0.1 to 100 mg/kg body weight orally in single or divided doses. For oral administration, the compositions can be provided in the form of tablets or

capsules containing 1.0 to 500 milligrams of the active ingredient, particularly 1, 5, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy. A suitable dosage range for oral administration of Compound A to humans is in a range of from about 25 mg to about 1000 mg per day (e.g., from about 100 mg to about 800 mg per patient once per day).

As noted above, the present invention is also directed to use of the HIV integrase inhibitor compounds of the present invention with one or more agents useful in the treatment of HIV infection or AIDS. For example, the compounds of this invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of one or more of the HIV/AIDS antivirals, imunomodulators, antiinfectives, or vaccines useful for treating HIV infection or AIDS. Suitable agents include those listed in the following Table:

ANTIVIRALS

Drug Name	Manufacturer (Tradename and/or Location)	Indication (Activity)
abacavir GW 1592 1592U89	Glaxo Welcome (ZIAGEN®)	HIV infection, AIDS, ARC (nucleoside reverse transcriptase inhibitor)
abacavir + lamivudine + zidovudine	GlaxoSmithKline (TRIZIVIR®)	HIV infection, AIDS, ARC (nucleoside reverse transcriptase inhibitors)
acemannan	Carrington Labs (Irving, TX)	ARC
ACH 126443	Achillion Pharm.	HIV infections, AIDS, ARC (nucleoside reverse transcriptase inhibitor)
acyclovir	Burroughs Wellcome	HIV infection, AIDS, ARC, in combination with AZT

AD-439	Tanox Biosystems	HIV infection, AIDS, ARC
AD-519	Tanox Biosystems	HIV infection, AIDS, ARC
adefovir dipivoxil GS 840	Gilead	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
AL-721	Ethigen (Los Angeles, CA)	ARC, PGL, HIV positive, AIDS
alpha interferon	GlaxoSmithKline	Kaposi's sarcoma, HIV, in combination w/Retrovir
AMD3100	AnorMed	HIV infection, AIDS, ARC (CXCR4 antagonist)
amprenavir 141 W94 GW 141 VX478 (Vertex)	GlaxoSmithKline (AGENERASE®)	HIV infection, AIDS, ARC (PI)
ansamycin LM 427	Adria Laboratories (Dublin, OH) Erbamont (Stamford, CT)	ARC
antibody which neutralizes pH labile alpha aberrant interferon	Advanced Biotherapy Concepts (Rockville, MD)	AIDS, ARC
AR177	Aronex Pharm	HIV infection, AIDS, ARC
atazanavir (BMS 232632)	Bristol-Myers Squibb (ZRIVADA®)	HIV infection, AIDS, ARC (protease inhibitor)
beta-fluoro-ddA	Nat'l Cancer Institute	AIDS-associated diseases
BMS-232623 (CGP-73547)	Bristol-Myers Squibb/ Novartis	HIV infection, AIDS, ARC (protease inhibitor)
BMS-234475 (CGP-61755)	Bristol-Myers Squibb/ Novartis	HIV infection, AIDS, ARC (protease inhibitor)
capravirine (AG-1549, S-1153)	Pfizer	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
CI-1012	Warner-Lambert	HIV-1 infection

cidofovir	Gilead Science	CMV retinitis, herpes, papillomavirus
curdlan sulfate	AJI Pharma USA	HIV infection
cytomegalovirus immune globin	MedImmune	CMV retinitis
cytovene ganciclovir	Syntex	sight threatening CMV peripheral CMV retinitis
delavirdine	Pharmacia-Upjohn (RESCRIPTOR®)	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
dextran Sulfate	Ueno Fine Chem. Ind. Ltd. (Osaka, Japan)	AIDS, ARC, HIV positive asymptomatic
ddC (zalcitabine, dideoxycytidine)	Hoffman-La Roche (HIVID®)	HIV infection, AIDS, ARC (nuclesodie reverse transcriptase inhibitor)
ddI dideoxyinosine	Bristol-Myers Squibb (VIDEX®)	HIV infection, AIDS, ARC; combination with AZT/d4T (nucleoside reverse transcriptase inhibitor)
DPC 681 & DPC 684	DuPont	HIV infection, AIDS, ARC (protease inhibitors)
DPC 961 & DPC 083	Bristol-Myers Squibb (from DuPont Pharma)	HIV infection AIDS, ARC (non-nucleoside reverse transcriptase inhibitors)
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
efavirenz (DMP 266)	Bristol-Myers Squibb (SUSTIVA®) Merck (STOCRIN®)	HIV infection, AIDS, ARC (non-nucleoside RT inhibitor)
famciclovir	Novartis (FAMVIR®)	herpes zoster, herpes simplex
emtricitabine FTC	Gilead (from Triangle Pharmaceuticals) (COVIRACIL®) Emory University	HIV infection, AIDS, ARC (nucleoside reverse transcriptase inhibitor)

emvirine	Gilead (from Triangle Pharmaceuticals) (COACTINON®)	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
enfuvirtide T-20	Trimeris & Roche (FUZEON®)	HIV infection, AIDS, ARC (fusion inhibitor)
HBY097	Hoechst Marion Roussel	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
hypericin	VIMRx Pharm.	HIV infection, AIDS, ARC
recombinant human interferon beta	Triton Biosciences (Almeda, CA)	AIDS, Kaposi's sarcoma, ARC
interferon alfa-n3	Interferon Sciences	ARC, AIDS
indinavir	Merck (CRIXIVAN®)	HIV infection, AIDS, ARC, asymptomatic HIV positive, also in combination with AZT/ddI/ddC
ISIS 2922	ISIS Pharmaceuticals	CMV retinitis
JE2147/AG1776	Agouron	HIV infection, AIDS, ARC (protease inhibitor)
KNI-272	Nat'l Cancer Institute	HIV-assoc. diseases
lamivudine, 3TC	GlaxoSmithKline (EPIVIR®)	HIV infection, AIDS, ARC (nucleoside reverse transcriptase inhibitor); also with AZT
lobucavir	Bristol-Myers Squibb	CMV infection
lopinavir (ABT-378)	Abbott	HIV infection, AIDS, ARC (protease inhibitor)
lopinavir + ritonavir (ABT-378/r)	Abbott (KALETRA®)	HIV infection, AIDS, ARC (protease inhibitor)
mozenavir (DMP-450)	AVID (Camden, NJ)	HIV infection, AIDS, ARC (protease inhibitor)
nelfinavir	Agouron (VIRACEPT®)	HIV infection, AIDS, ARC (protease inhibitor)
nevirapine	Boeheringer Ingleheim (VIRAMUNE®)	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)

novapren	Novaferon Labs, Inc. (Akron, OH)	HIV inhibitor
peptide T octapeptide sequence	Peninsula Labs (Belmont, CA)	AIDS
PRO 140	Progenics	HIV infection, AIDS, ARC (CCR5 co-receptor inhibitor)
PRO 542	Progenics	HIV infection, AIDS, ARC (attachment inhibitor)
trisodium phosphonoformate	Astra Pharm. Products, Inc	CMV retinitis, HIV infection, other CMV infections
PNU-140690	Pharmacia Upjohn	HIV infection, AIDS, ARC (protease inhibitor)
probucol	Vyrex	HIV infection, AIDS
RBC-CD4	Sheffield Med. Tech (Houston TX)	HIV infection, AIDS, ARC
ritonavir (ABT-538)	Abbott (RITONAVIR®)	HIV infection, AIDS, ARC (protease inhibitor)
saquinavir	Hoffmann-LaRoche (FORTOVASE®)	HIV infection, AIDS, ARC (protease inhibitor)
stavudine; d4T didehydrodeoxy-thymidine	Bristol-Myers Squibb (ZERIT®)	HIV infection, AIDS, ARC (nucleoside reverse transcriptase inhibitor)
T-1249	Trimeris	HIV infection, AIDS, ARC (fusion inhibitor)
TAK-779	Takeda	HIV infection, AIDS, ARC (injectable CCR5 receptor antagonist)
tenofovir	Gilead (VIREAD®)	HIV infection, AIDS, ARC (nucleotide reverse transcriptase inhibitor)
tipranavir (PNU-140690)	Boehringer Ingelheim	HIV infection, AIDS, ARC (protease inhibitor)
TMC-120 & TMC-125	Tibotec	HIV infections, AIDS, ARC (non-nucleoside reverse transcriptase inhibitors)

TMC-126	Tibotec	HIV infection, AIDS, ARC (protease inhibitor)
valaciclovir	GlaxoSmithKline	genital HSV & CMV infections
virazole ribavirin	Viratek/ICN (Costa Mesa, CA)	asymptomatic HIV positive, LAS, ARC
zidovudine; AZT	GlaxoSmithKline (RETROVIR®)	HIV infection, AIDS, ARC, Kaposi's sarcoma in combination with other therapies (nucleoside reverse transcriptase inhibitor)

IMMUNO-MODULATORS

Drug Name	Manufacturer	Indication
AS-101	Wyeth-Ayerst	AIDS
Bropirimine	Pharmacia Upjohn	advanced AIDS
Acemannan	Carrington Labs, Inc. (Irving, TX)	AIDS, ARC
CL246,738	American Cyanamid Lederle Labs	AIDS, Kaposi's sarcoma
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
FP-21399	Fuki ImmunoPharm	blocks HIV fusion with CD4+ cells
Gamma Interferon	Genentech	ARC, in combination w/TNF (tumor necrosis factor)
Granulocyte Macrophage Colony Stimulating Factor	Genetics Institute Sandoz	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Hoeschst-Roussel Immunex	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Schering-Plough	AIDS, combination w/AZT
HIV Core Particle Immunostimulant	Rorer	seropositive HIV
IL-2 Interleukin-2	Cetus	AIDS, in combination w/AZT

IL-2 Interleukin-2	Hoffman-La Roche Immunex	AIDS, ARC, HIV, in combination w/AZT
IL-2 Interleukin-2 (aldeslukin)	Chiron	AIDS, increase in CD4 cell counts
Immune Globulin ntravenous (human)	Cutter Biological (Berkeley, CA)	pediatric AIDS, in combination w/AZT
IMREG-1	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
IMREG-2	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
Imuthiol Diethyl Dithio Carbamate	Merieux Institute	AIDS, ARC
Alpha-2 Interferon	Schering Plough	Kaposi's sarcoma w/AZT, AIDS
Methionine- Enkephalin	TNI Pharmaceutical (Chicago, IL)	AIDS, ARC
MTP-PE Muramyl-Tripeptide	Ciba-Geigy Corp.	Kaposi's sarcoma
Granulocyte Colony Stimulating Factor	Amgen	AIDS, in combination w/AZT
Remune	Immune Response Corp.	immunotherapeutic
rCD4 Recombinant Soluble Human CD4	Genentech	AIDS, ARC
rCD4-IgG hybrids		AIDS, ARC
Recombinant Soluble Human CD4	Biogen	AIDS, ARC
Interferon Alfa 2a	Hoffman-La Roche	Kaposi's sarcoma, AIDS, ARC, in combination w/AZT
SK&F106528 Soluble T4	Smith Kline	HIV infection
Thymopentin	Immunobiology Research Institute	HIV infection
Tumor Necrosis Factor; TNF	Genentech	ARC, in combination w/gamma Interferon
etanercept	Immunex Corp (ENBREL®)	rheumatoid arthritis

infliximab	Centocor (REMICADE®)	rheumatoid arthritis and Crohn's disease

ANTI-INFECTIVES

Drug Name	Manufacturer	Indication
Clindamycin with Primaquine	Pharmacia Upjohn	PCP
Fluconazole	Pfizer	cryptococcal meningitis, candidiasis
Pastille Nystatin Pastille	Squibb Corp.	prevention of oral candidiasis
Ornidyl Eflornithine	Merrell Dow	PCP
Pentamidine Isethionate (IM & IV)	LyphoMed (Rosemont, IL)	PCP treatment
Trimethoprim		antibacterial
Trimethoprim/sulfa		antibacterial
Piritrexim	Burroughs Wellcome	PCP treatment
Pentamidine isethionate for inhalation	Fisons Corporation	PCP prophylaxis
Spiramycin	Rhone-Poulenc	cryptosporidia diarrhea
Intraconazole-R51211	Janssen Pharm.	histoplasmosis; cryptococcal meningitis
Trimetrexate	Warner-Lambert	PCP

OTHER

Drug Name	Manufacturer	Indication
Daunorubicin	NeXstar, Sequus	Karposi's sarcoma
Recombinant Human Erythropoietin	Ortho Pharm. Corp.	severe anemia assoc. with AZT therapy
Recombinant Human Growth Hormone	Serono	AIDS-related wasting, cachexia
Leukotriene B4 Receptor Antagonist	-	HIV infection

Megestrol Acetate	Bristol-Myers Squibb	treatment of anorexia assoc. w/AIDS
Soluble CD4 Protein and Derivatives	-	HIV infection
Testosterone	Alza, Smith Kline	AIDS-related wasting
Total Enteral Nutrition	Norwich Eaton Pharmaceuticals	diarrhea and malabsorption, related to AIDS

It will be understood that the scope of combinations of the compounds of this invention with HIV/AIDS antivirals, immunomodulators, anti-infectives or vaccines is not limited to the list in the above Table, but includes in principle any combination with any pharmaceutical composition useful for the treatment of AIDS. The HIV/AIDS antivirals and other agents will typically be employed in these combinations in their conventional dosage ranges and regimens as reported in the art, including the dosages described in the Physicians' Desk Reference, 54th edition, Medical Economics Company, 2000, which is incorporated herein by reference in its entirety. The dosage ranges for a compound of the invention in these combinations are the same as those set forth above.

Abbreviations used in the instant specification, particularly the Schemes and Examples, include the following:

AIDS = acquired immunodeficiency syndrome

APCI = atmospheric pressure chemical ionization mass spectroscopy

ARC = AIDS related complex

BOC or Boc = t-butyloxycarbonyl

BOP = benzotriazol-1-yloxytris-(dimethylamino)phosphonium hexafluorophosphate

t-Bu = tert-butyl

n-BuLi = n-butyllithium

DEAD = diethylazodicarboxylate

DIPA = diisopropylamine

DMF = dimethylformamide

DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone

DMSO = dimethyl sulfoxide

dppf = 1,1'-bis(diphenylphosphino)ferrocene

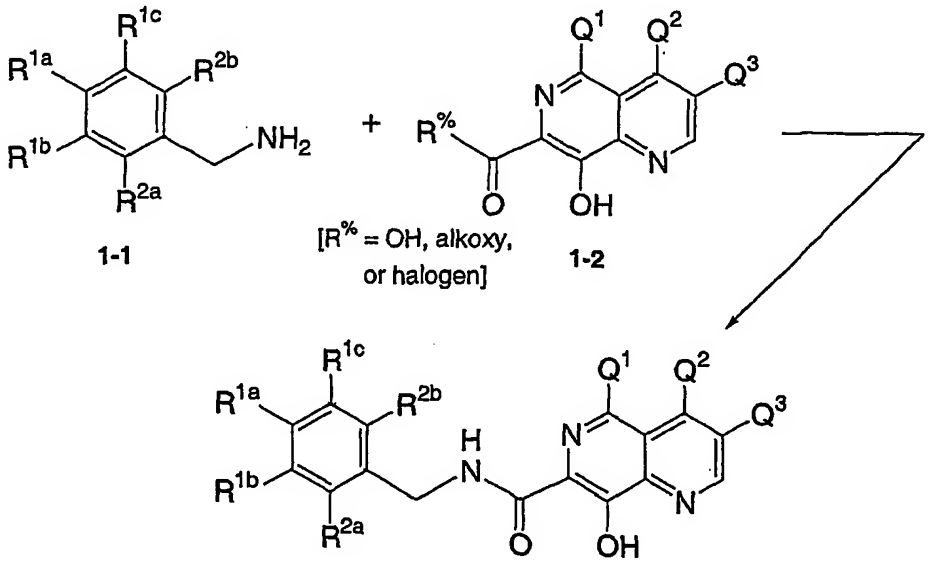
EDC or EDAC = 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
EDTA = ethylenediaminetetraacetic acid
ES-MS = eletron spray mass spectroscopy
Et = ethyl
EtOAc = ethyl acetate
HIV = human immunodeficiency virus
HOAT = 1-hydroxy-7-azabensotriazole
HOBt = 1-hydroxy benzotriazole hydrate
HPLC = high performance liquid chromatography
HRMS = high resolution mass spectroscopy
KF = Karl Fisher titration for water
LC = liquid chromatography
Me = methyl
MeOH = methanol
Ms = mesyl or methanesulfonyl
MS = mass spectroscopy
MTBE = methyl tert-butyl ether
NBS = N-bromosuccinimide
NIS = N-iodosuccinimide
NMM = N-methyl morpholine
NMR = nuclear magnetic resonance
Ph = phenyl
PMBCl = *p*-methoxybenzyl chloride
Pr = propyl
TEA = triethylamine
Tf_2O = triflic anhydride
TFA = trifluoroacetic acid
TsCl = toluenesulfonyl chloride
THF = tetrahydrofuran
TLC = thin layer chromatography
UV = ultraviolet

The compounds of the present invention can be readily prepared according to the following reaction schemes and examples, or modifications thereof, using readily available starting materials, reagents and conventional synthesis

procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail. Furthermore, other methods for preparing compounds of the invention will be readily apparent to the person of ordinary skill in the art in light of the following reaction schemes and examples. Unless otherwise indicated, all variables are as defined above.

The compounds of the present invention can be prepared by the coupling of suitable 1,6-naphthyridine-7-carboxylic acids (or acid derivatives such as acid halides or esters) with the appropriate benzylamines. Scheme 1 depicts the coupling reaction to obtain compounds of Formula (III). (Note: The schemes depict and/or illustrate methods for preparing compounds of Formula (III), but the schemes also apply with a suitable choice of reactants to the preparation of compounds of Formula (I) and Formula (II) and any other compounds of the present invention -- e.g., compounds of Formula (I) of the present invention can be prepared in accordance with Scheme 1 by employing an appropriate amine **1-1** (i.e., R^{1a} is replaced with R^1, R^{2a} is replaced with R^2, and R^{1b}, R^{1c} and R^{2b} are all H) and an appropriate naphthyridine **1-2** (i.e., Q^1 is replaced with R^3, and Q^2 and Q^3 are both H).)

SCHEME 1

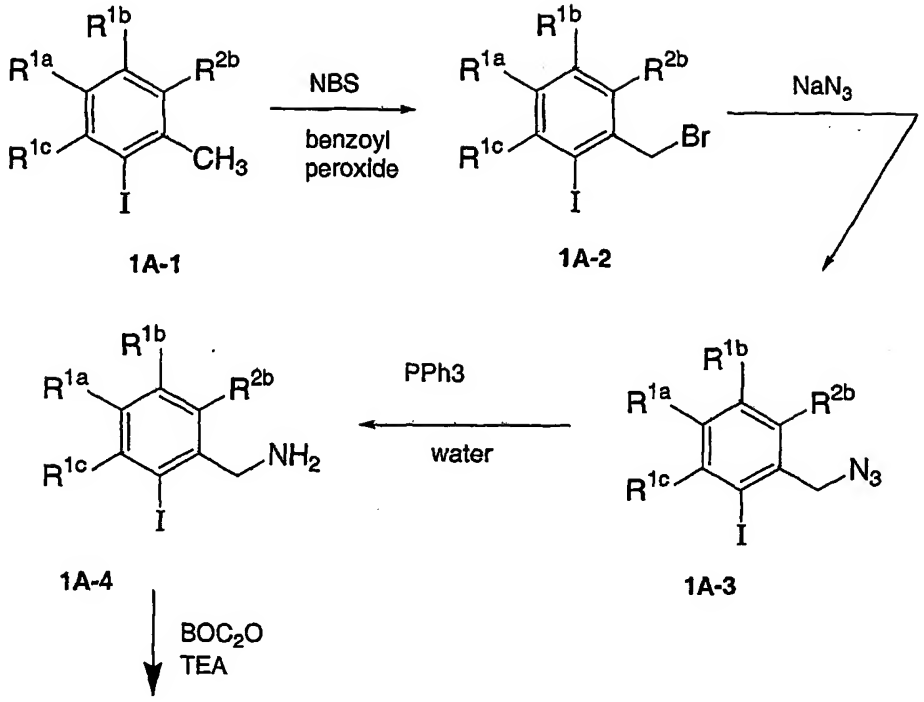


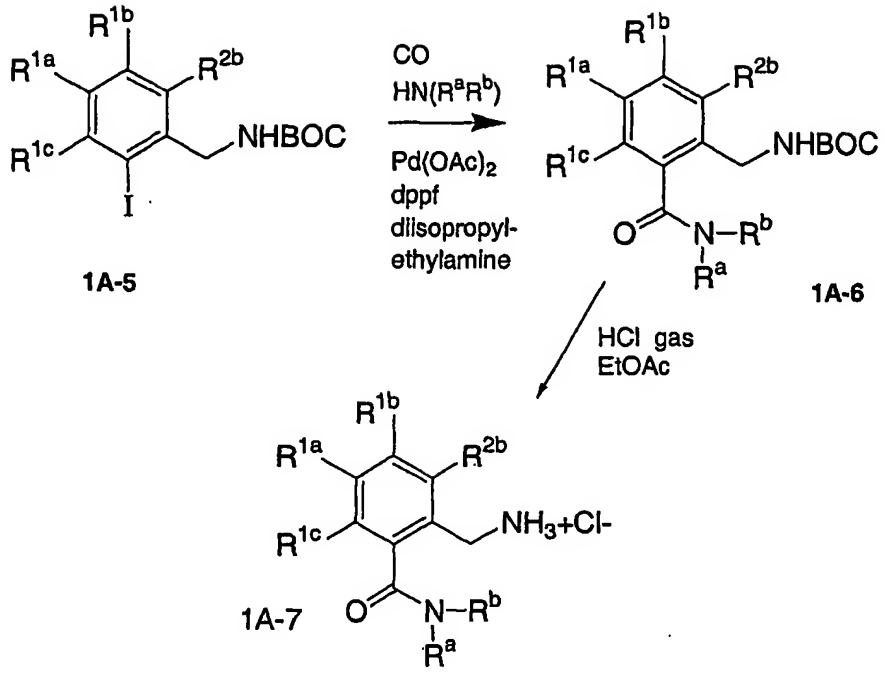
Compound III

Methods for coupling carboxylic acids with amines to form carboxamides are well known in the art. Suitable methods are described, for example, in Jerry March, Advanced Organic Chemistry, 3rd edition, John Wiley & Sons, 1985, pp. 370-376, or in M. Bodanszky, The Practice of Peptide Synthesis, Springer-Verlag, 1984. Amines of formula **1-1** can be prepared, for example, by the reaction of a suitable benzyl halide with ammonia, by conversion of a suitable benzyl halide with hexamethylenetetramine, by treating the halide with potassium phthalimide and hydrolyzing the product, and by converting a benzyl halide to an azide and then reducing the azide to an amine; which methods are described, for example, in Jerry March, Advanced Organic Chemistry, 3rd edition, John Wiley & Sons, 1985, pp. 364-365, 366, 377-378, 380, and 1106. Amines of formula **1-1** can also be prepared using, for example, the methods described in Richard Larock, Comprehensive Organic Transformations, 2nd edition,Wiley-VCH Publishers Inc, 1999, pp 753-879, or routine variations thereof. Naphthyridine carboxylic acids of formula **1-2** can be prepared using methods described in Ochiai et al., *Chem.Ber.* 1937, 70: 2018, 2023; and Albert et al., *J.Chem.Soc.* 1952, 4985, 4991; or routine variations thereof. The schemes set forth below illustrate and expand upon the chemistry portrayed in Scheme 1.

Scheme 1A depicts a method for preparing benzylamine reactants having at least one ortho-aminocarbonyl group on the benzyl ring. Substituted toluene **1A-1** is functionalized on the methyl group via radical bromination to give the bromide **1A-2**. Radical brominations are well known in the art and are described, for example, in J. March, Advanced Organic Chemistry, 3rd edition, John Wiley & Sons, 1985, p. 625. The azide **1A-3** can then be obtained by displacement of the bromide with azide (see J. March, Advanced Organic Chemistry, 3rd edition, John Wiley & Sons, 1985, p. 380), followed by reduction of the azide using triphenylphosphine and water to afford the amine **1A-4**. Similar reductions are described in *Tetrahedron* 2000, 56(52): 10175-10184; in *J. Am. Chem. Soc.* 2001, 123(5): 875-885; and in Zhou, *Tett Lett.* 1999, 40: 2729. Following protection of the amino group on **1A-4** using BOC, the iodide can be transformed into the carboxyamide **1A-6** through a palladium-catalyzed carbonylation reaction in the presence of a suitable amine, in a manner similar to that described in G. Ortar, *Tett. Lett.* 1986, 27: 3931. Following removal of the BOC group, amine **1A-7** can be coupled to a suitable naphthyridine carboxylic acid, e.g., with EDC and HOAt in the presence of a suitable base such as triethylamine.

SCHEME 1A

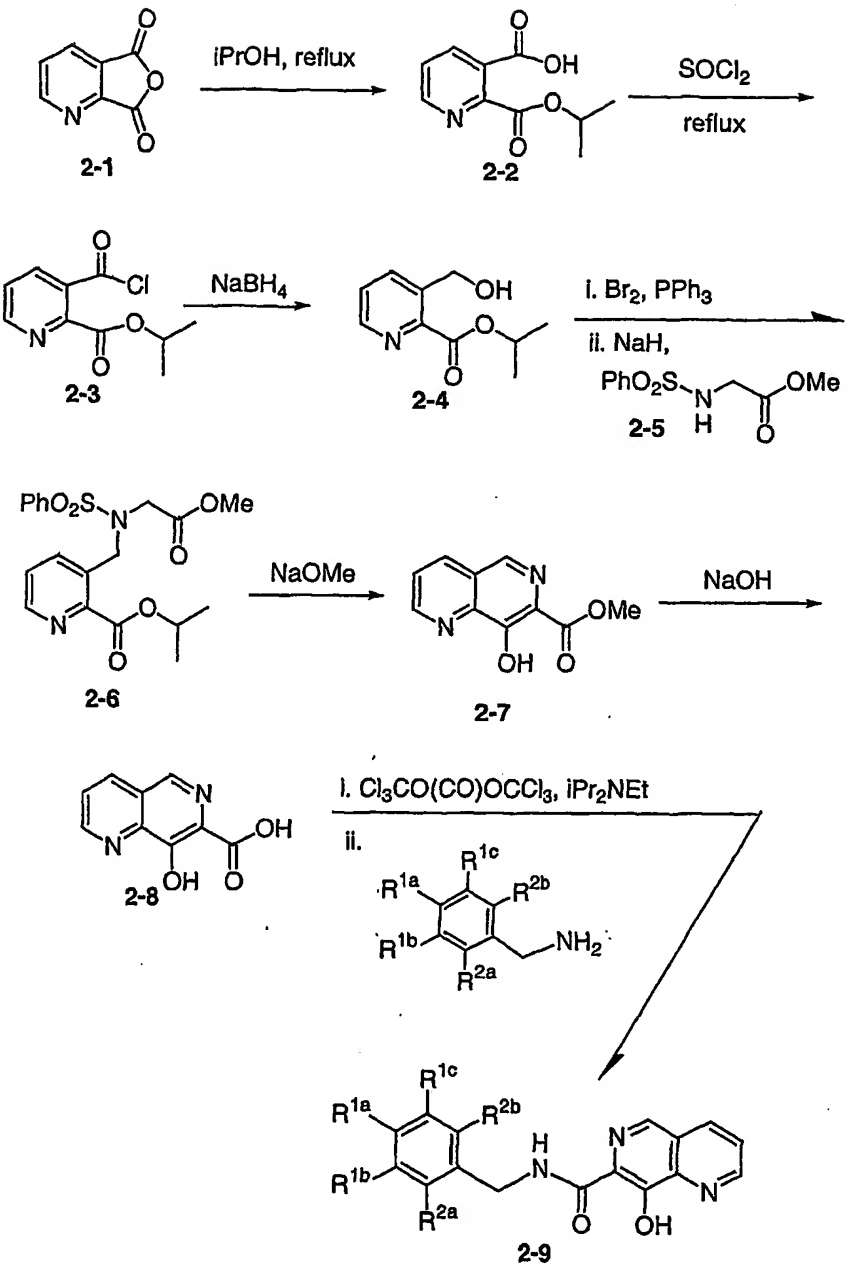

R1b
R1a
R2b
R1c
CH3
I
NBS
benzoyl peroxide
Br
NaN3
1A-1
1A-2
PPh3
water
NH2
N3
1A-4
1A-3
BOC2O
TEA



In Scheme 2, following the procedure set forth in Ornstein et al., *J. Med. Chem.* 1989, 32: 827-833, quinolinic anhydride **2-1** can be opened with isopropanol to provide mono acid **2-2**, which can be converted to the corresponding acyl chloride **2-3** (e.g., by refluxing thionyl chloride). Acyl chloride **2-3** can then be reduced (e.g., with $NaBH_4$ or $LiBH_4$) to the corresponding alcohol **2-4**, which can be converted to the corresponding bromide through the action of bromine in the presence of triphenylphosphine. Alkylation of the bromide with the sodium anion of phenylsulfonamide **2-5** in a polar aprotic solvent like DMF can provide sulfonamide **2-6**, which can be treated with a base (e.g., alkali metal alkoxide such as sodium methoxide) to provide the bicyclic ester **2-7** via a Dieckmann cyclization. Saponification of the ester (e.g., with aqueous NaOH at reflux) will afford the acid **2-8**. The acid **2-8** can be activated with triphosgene and coupled with a variety of benzylamines to provide the compounds of the invention **2-9**.

The starting anhydrides of formula **2-1** can be prepared via methods described in Philips et al., *Justus Liebigs Ann. Chem.* 1895, 288: 2535; Bernthsen et al., *Chem.Ber.* 1887; 20: 1209; Bly et al., *J.Org.Chem.* 1964, 29: 2128-2135; and Krapcho et al., *J.Heterocycl.Chem.* 1993, 30: 1597-1606; or routine variations thereof.

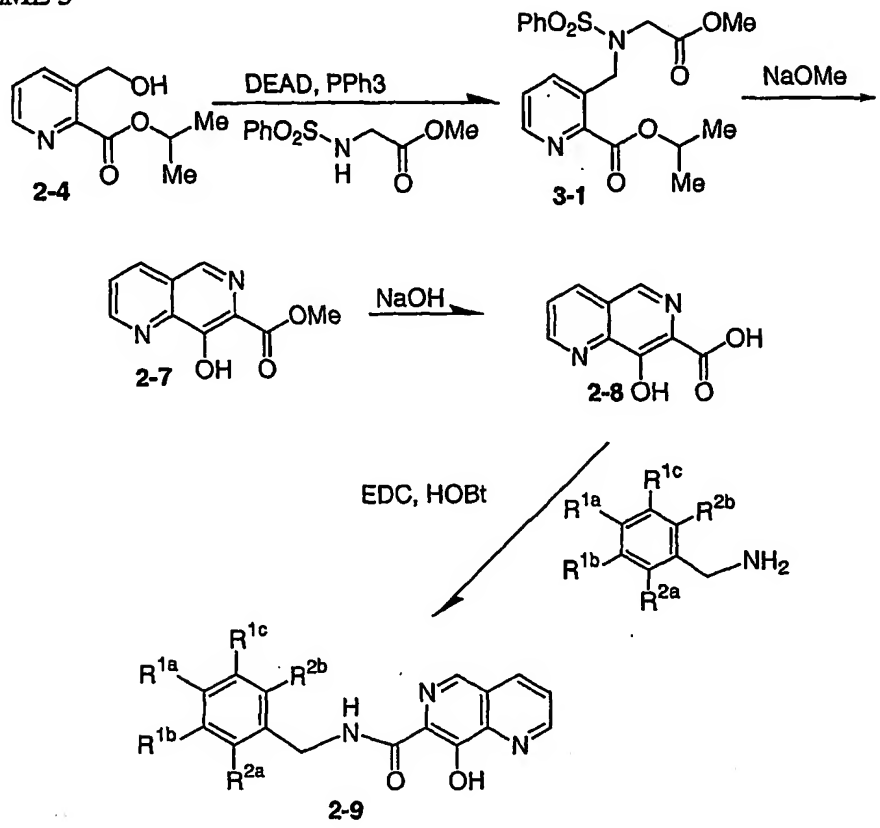
SCHEME 2



Scheme 3 depicts an alternative synthesis in which alcohol **2-4** can undergo the Mitsunobu reaction with the phenylsulfonamide of glycine methyl ester to provide **3-1**. The sulfonamide **3-1** can again be elaborated to provide the acid **2-8**,

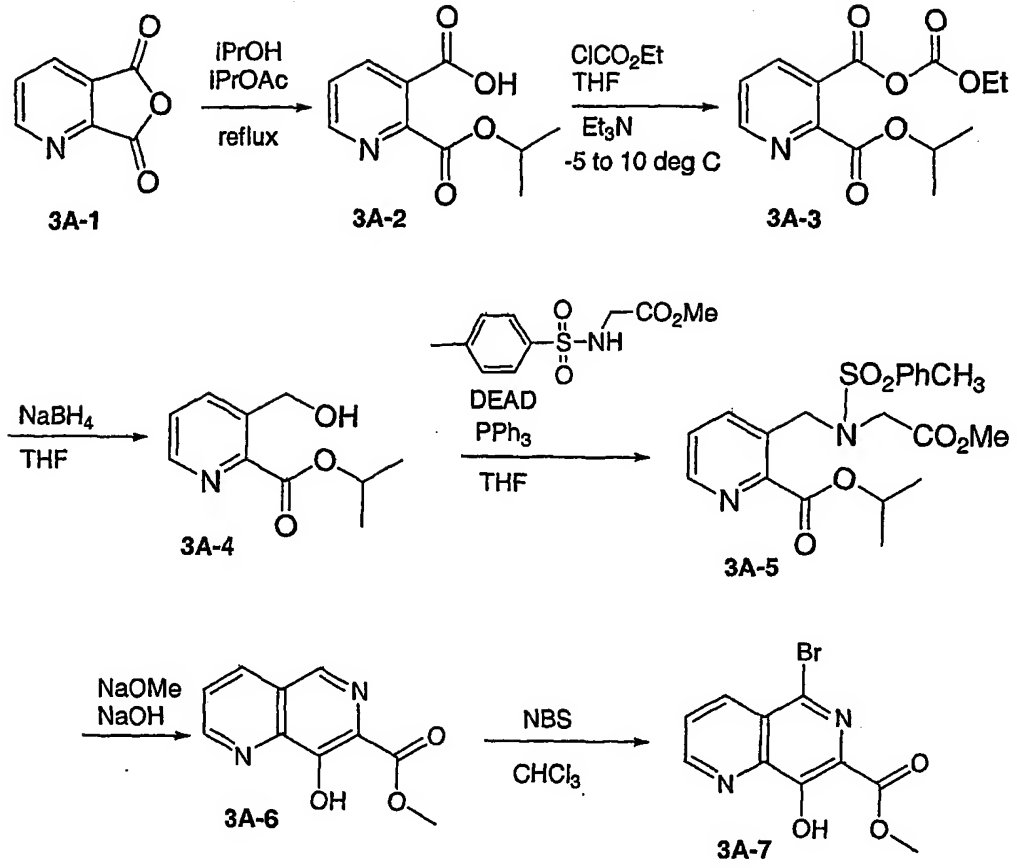
which can be coupled with a variety of amines using standard reagents to provide the compounds of the invention **2-9**.

SCHEME 3



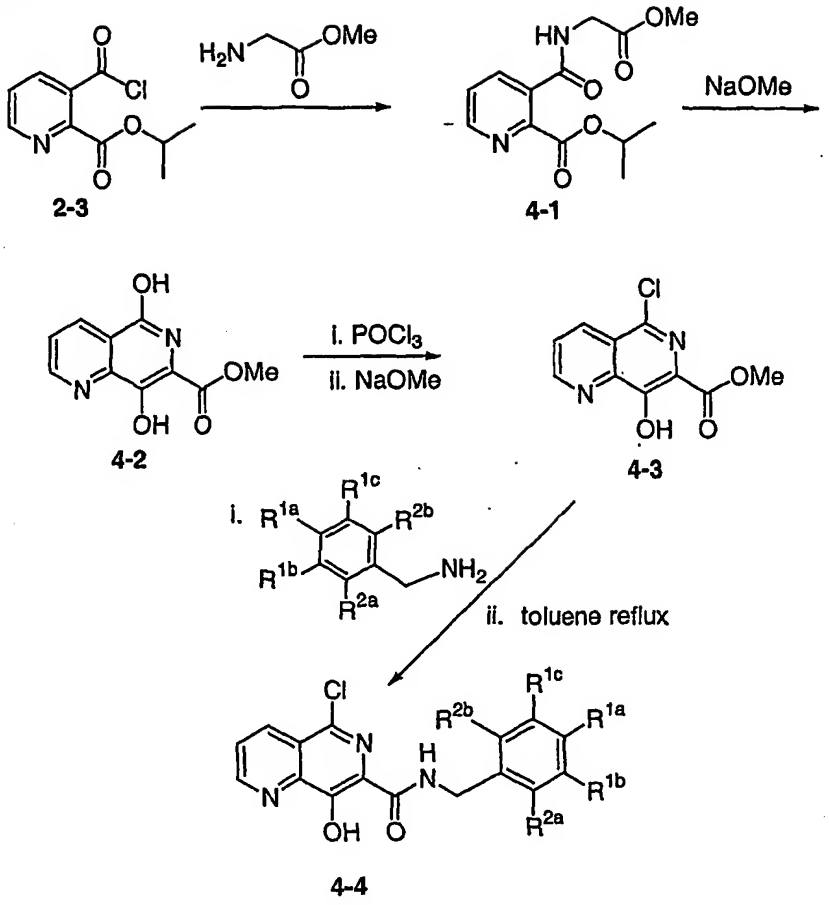
Scheme 3A depicts a variation of the synthesis shown in Scheme 3, wherein the acid **3A-2** is reacted with ethyl chloroformate to form the mixed anhydride **3A-3**, which is reduced to alcohol **3A-4**. Alcohol **3A-4** can undergo the Mitsunobu reaction with methyl tosylglycine to form the ester **3A-5**, which under treatment with base cyclizes to form the 1,6-naphthyridine **3A-6**. Bromination then yields the bromoester **3A-7**.

Scheme 3A



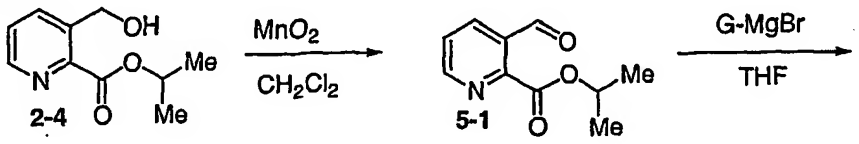
Halogen substituted compounds of the present invention can be prepared as shown in Scheme 4. The acid chloride **2-3** can be reacted with glycine methyl ester to provide the amide **4-1**. Dieckmann cyclization of the ester **4-1** with a sodium alkoxide base in an alcoholic solvent like methanol will provide phenol **4-2**., which can be reacted with phosphorous oxychloride, followed by methanolysis of the intermediate phosphonate esters to provide **4-3**. The ester bond of **4-3** can react selectively with suitable amines in refluxing nonpolar aromatic solvents (e.g., toluene) to provide the corresponding halogenated derivative **4-4**.

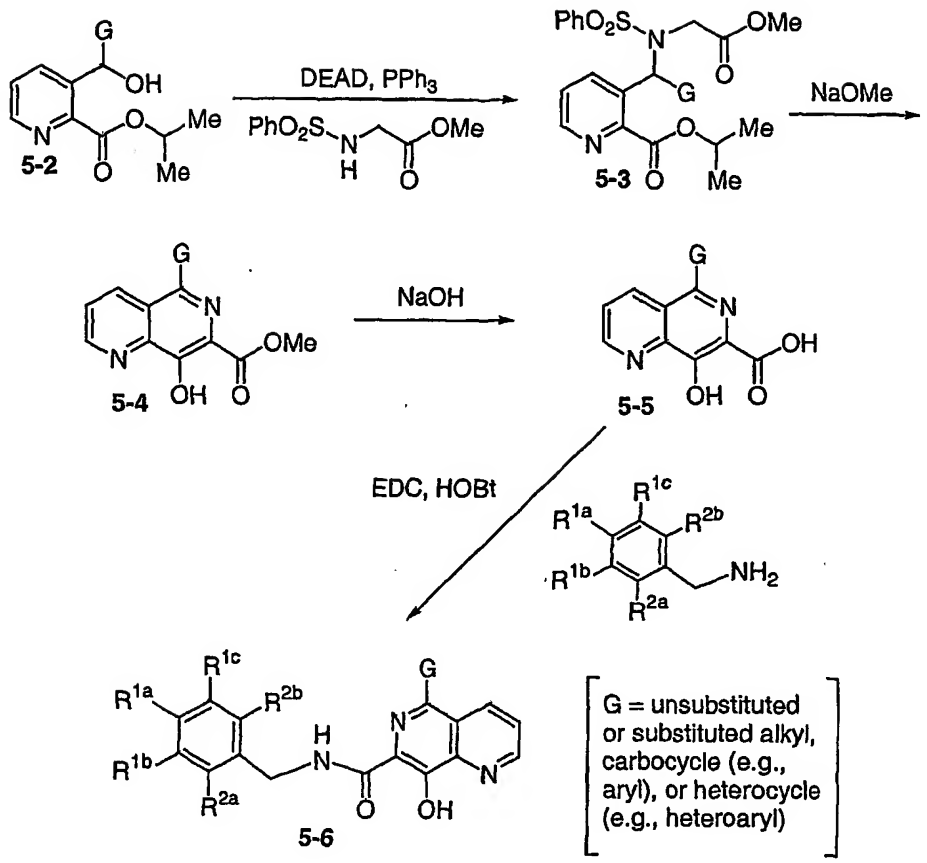
SCHEME 4



The preparation of compounds that feature additional substituents can be achieved in accordance with Scheme 5. Oxidation of the alcohol **2-4** with manganese dioxide in an inert solvent such as methylene chloride will provide aldehyde **5-1**. The addition of Grignard reagents (such as phenyl magnesium bromide) to aldehyde moiety **5-1** can occur regioselectively to provide the alcohol **5-2**, which can then be elaborated to the compounds of the invention **5-6**.

SCHEME 5



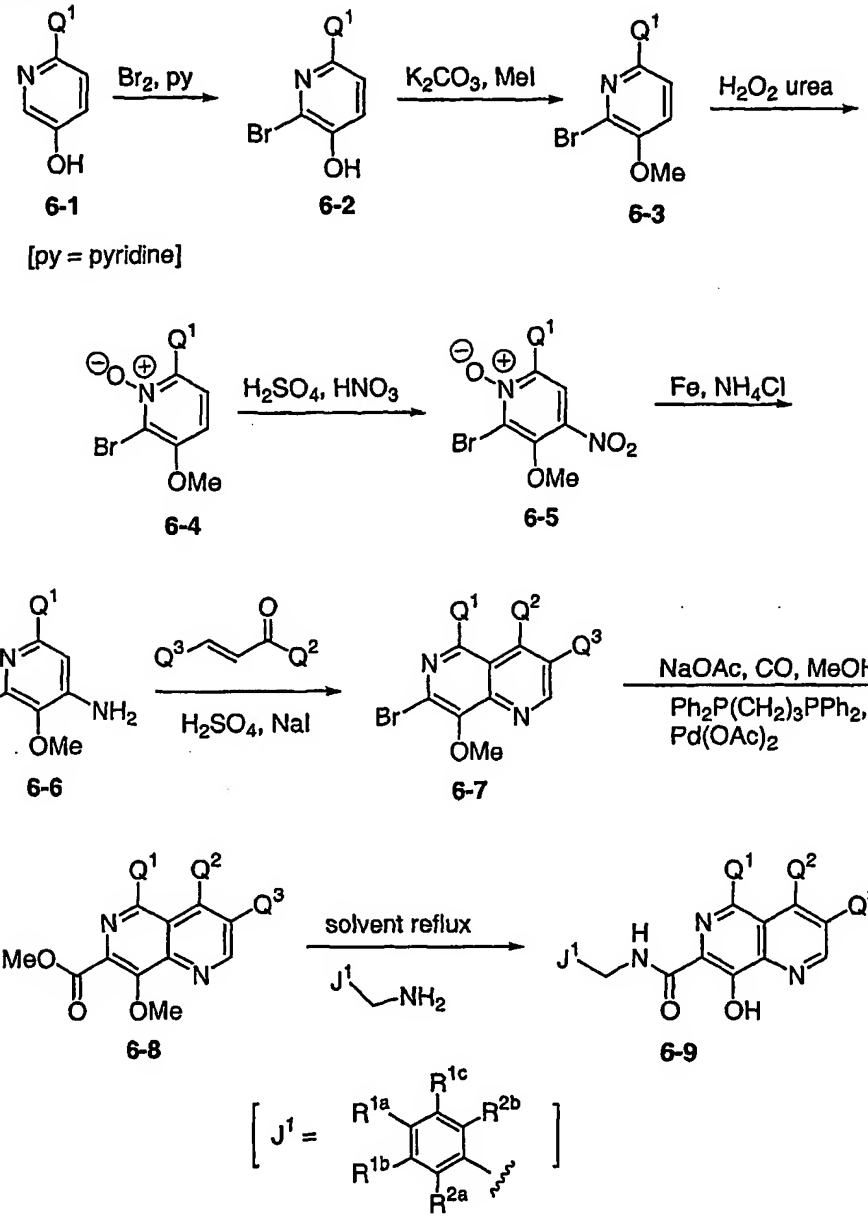


A further synthetic route to prepare compounds that are the subject of the invention is shown in Scheme 6. This methodology allows access to naphthyridine derivatives that are substituted at the 3, 4 and 5 positions. Briefly, a 2-substituted 5-hydroxypyridine derivative **6-1** can be treated with bromine to undergo bromination at the 6 position to afford **6-2**, which can be converted to the methoxypyridine **6-3** and then oxidized to the corresponding N-oxide **6-4**. The N-oxide can be nitrated to provide **6-5**. Reduction of **6-5** with iron in the presence of ammonium chloride can provide the aniline **6-6**, which can be reacted with an alpha,beta-unsaturated aldehyde or ketone in the presence of an acid catalyst like sulfuric acid to provide **6-7** via an annulation. The bromide **6-7** can be elaborated to the amide **6-9** via a sequence of carbonylation and amidation reactions.

2-Substituted 5-hydroxypyridine derivatives of formula **6-1** can be prepared via methods described in Sorm et al., *Collect.Czech.Chem..Commun..*1949,

14: 331,342; and Saksena et al., *Tetrahedron Lett.*1993, 34: 3267-3270: or routine variations thereof.

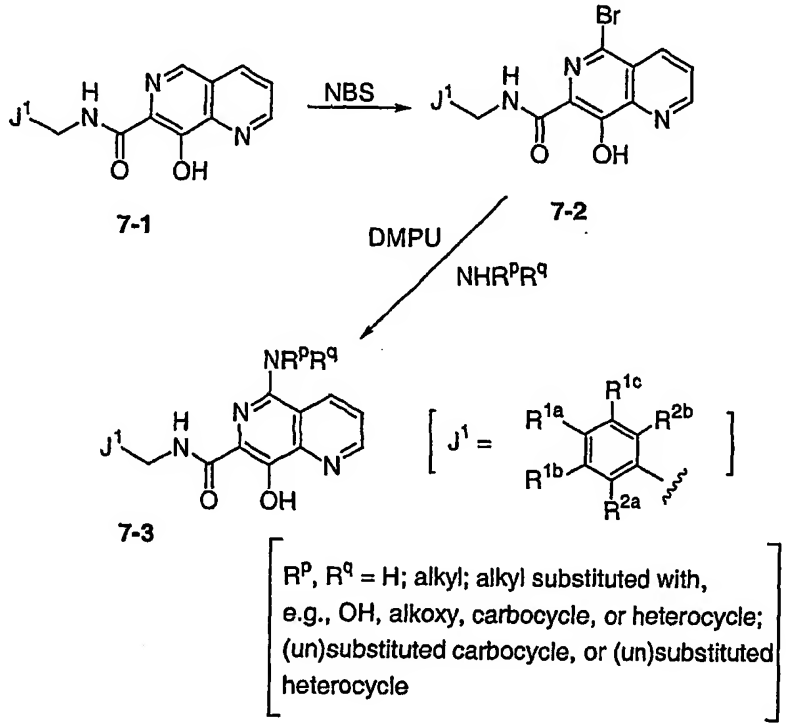
SCHEME 6



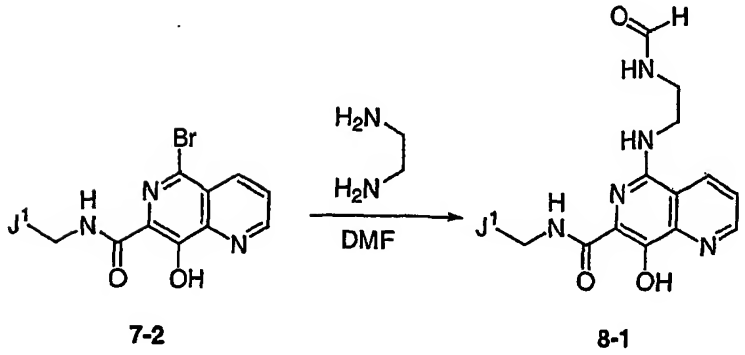
Compounds of the invention that comprise an amino substituent at the 5 position can be prepared in the manner set forth in Schemes 7 and 8. Bromination

of the phenol **7-1** occurs regioselectively upon treatment with NBS in an inert solvent like methylene chloride to afford **7-2**. Reaction of this bromide with an amine at elevated temperatures in the presence of a polar solvent such as DMPU affords compounds of the invention **7-3**. Similar reaction of the bromide **7-2** (Scheme 8) with a diamine such as ethylene diamine in DMF as solvent will afford the formylated derivative **8-1** in addition to the expected diaminoethane derivative.

SCHEME 7

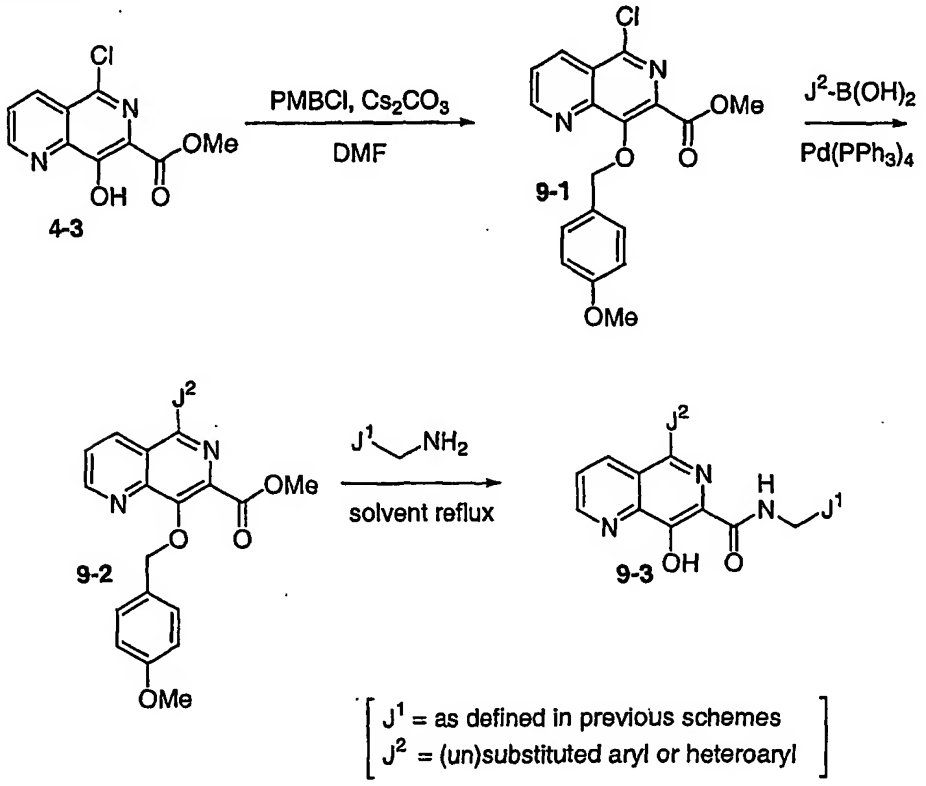


SCHEME 8



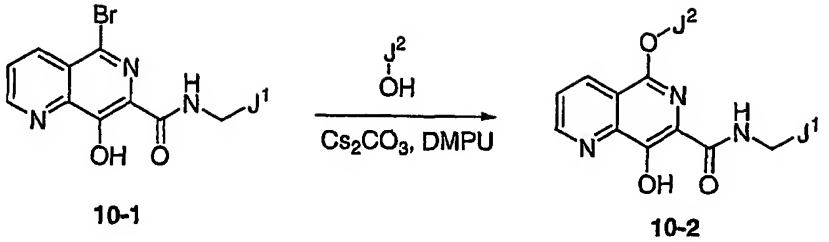
Preparation of aryl and heteroaryl derivatives via palladium cross coupling of the chloride **9-1** and the requisite boronic acids are depicted in Scheme 9.

SCHEME 9

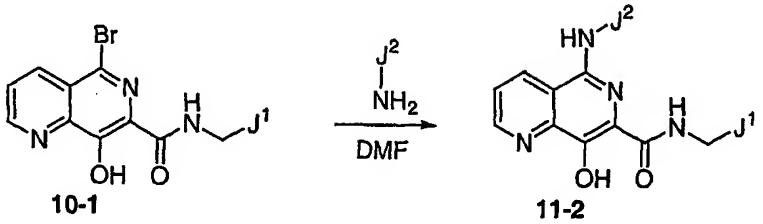


(Hetero)aryloxy, (hetero)arylamino, and (heteroaryl)thioxy derivatives **10-2**, **11-2**, and **12-2** respectively can be prepared as shown in Schemes 10 to 12. The corresponding sulfone derivatives **12-2** can be obtained by oxidation of the sulfides **12-1** with either ozone or 3-chloroperbenzoic acid as shown in Scheme 12.

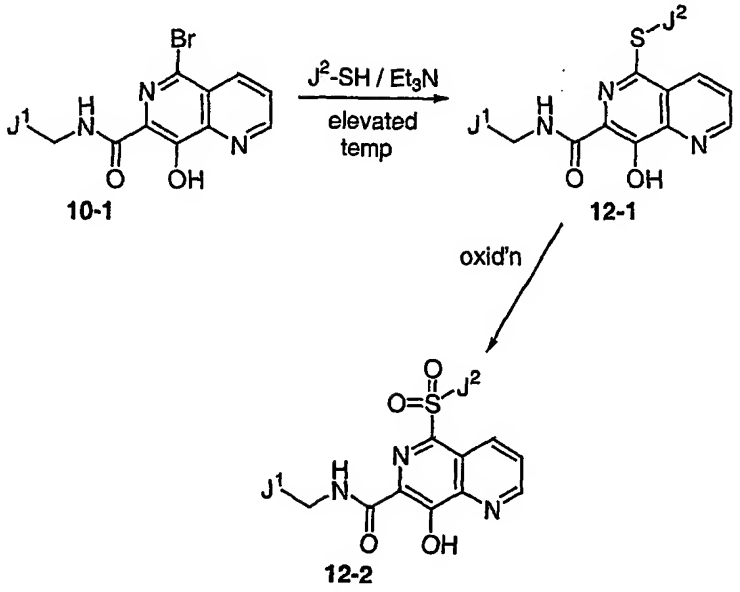
SCHEME 10



SCHEME 11



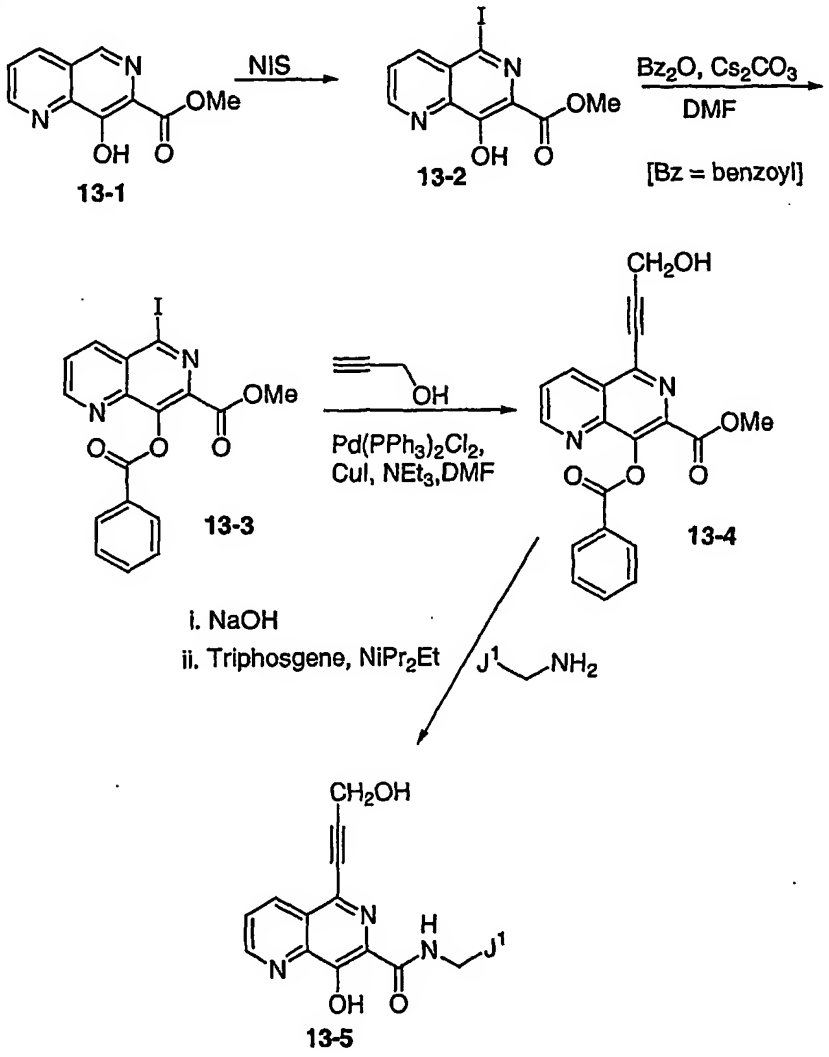
SCHEME 12



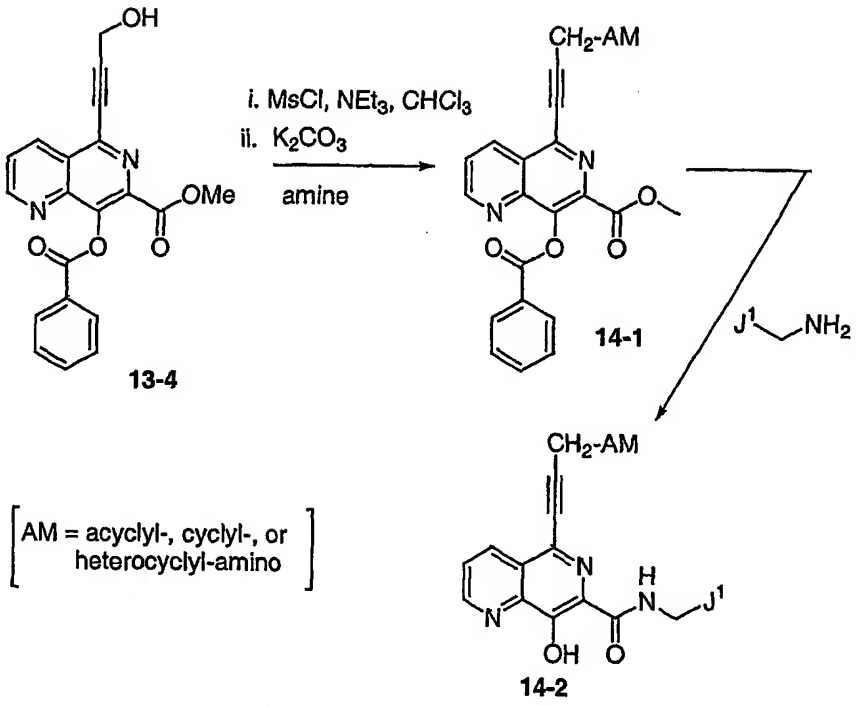
Preparation of compounds of the invention substituted with an acetylene can be prepared according to Scheme 13, which exemplifies the procedure for the naphthyridine core. Following protection of the iodide **13-2** as its benzoate **13-3**, the acetylenic group (for example propynol) can be appended by employing a suitable palladium catalyst in the presence of copper iodide. Aminolysis of the ester

13-4 will afford the amide **13-5** with concomitant deprotection of the benzoate ester. Alternately the ester **13-4** can be converted to the corresponding amine and sulfone derivatives as shown in Schemes 14 and 15. Scheme 16 shows that the preparation of the nitrile derivative **16-2** can be achieved via a palladium catalyzed cyanation of the iodide **13-4**.

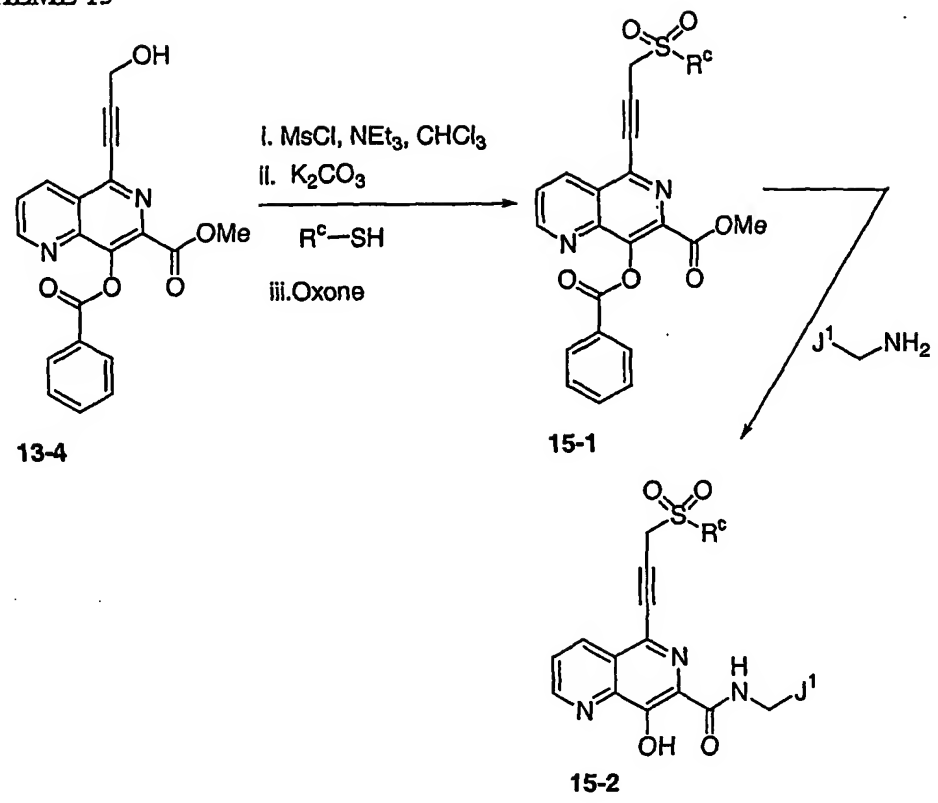
SCHEME 13



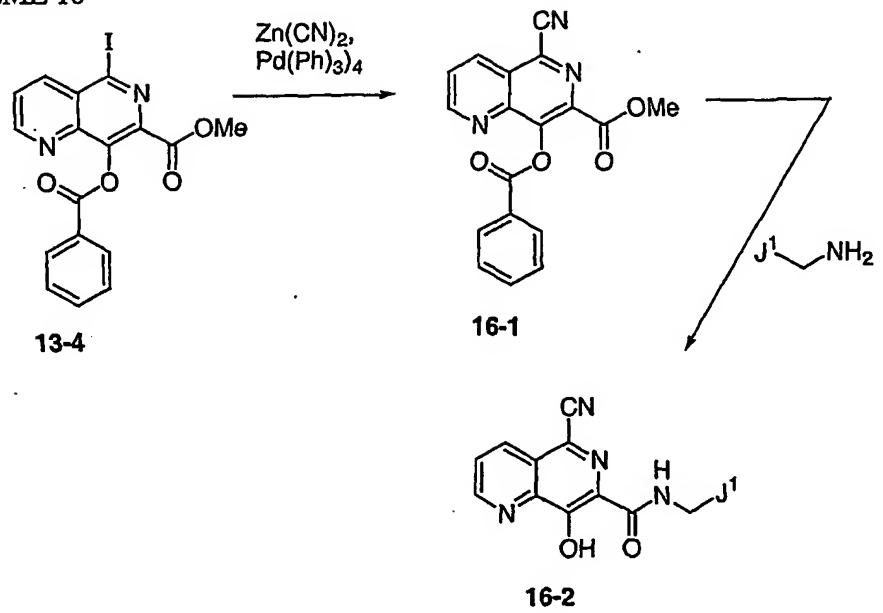
SCHEME 14


OH
OMe
i. MsCl, NEt3, CHCl3
ii. K2CO3
amine
CH2-AM
13-4
14-1
J1
NH2
CH2-AM
AM = acyclyl-, cyclyl-, or heterocyclyl-amino
14-2

SCHEME 15

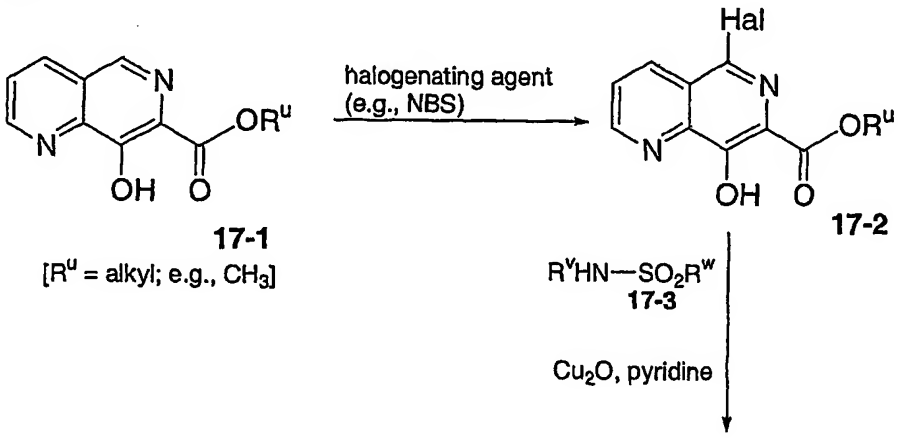


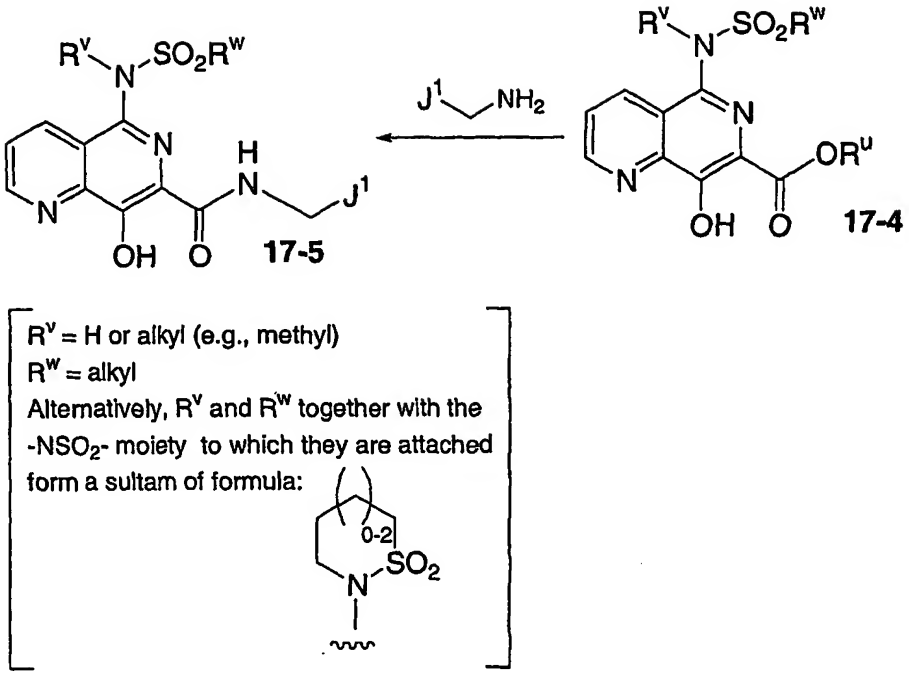
SCHEME 16



Preparation of compounds of the invention substituted with a sulfonamide can be prepared according to Scheme 17. The preparation includes halogenation of alkyl 8-hydroxy-naphthyridine carboxylate **17-1** with a halogenation agent such as N-bromosuccinimide, and then condensing the 5-halo-8-hydroxy-naphthyridine carboxylic ester **17-2** with sulfonamide **17-3** at elevated temperature (e.g., about 120 °C) in the presence of a copper promoter (e.g., copper(I) oxide) to afford sulfonamidonaphthyridine **17-4**. The 7-position ester can then be hydrolyzed and the benzylamine portion attached through standard amide bond formation methods to give desired product **17-6**.

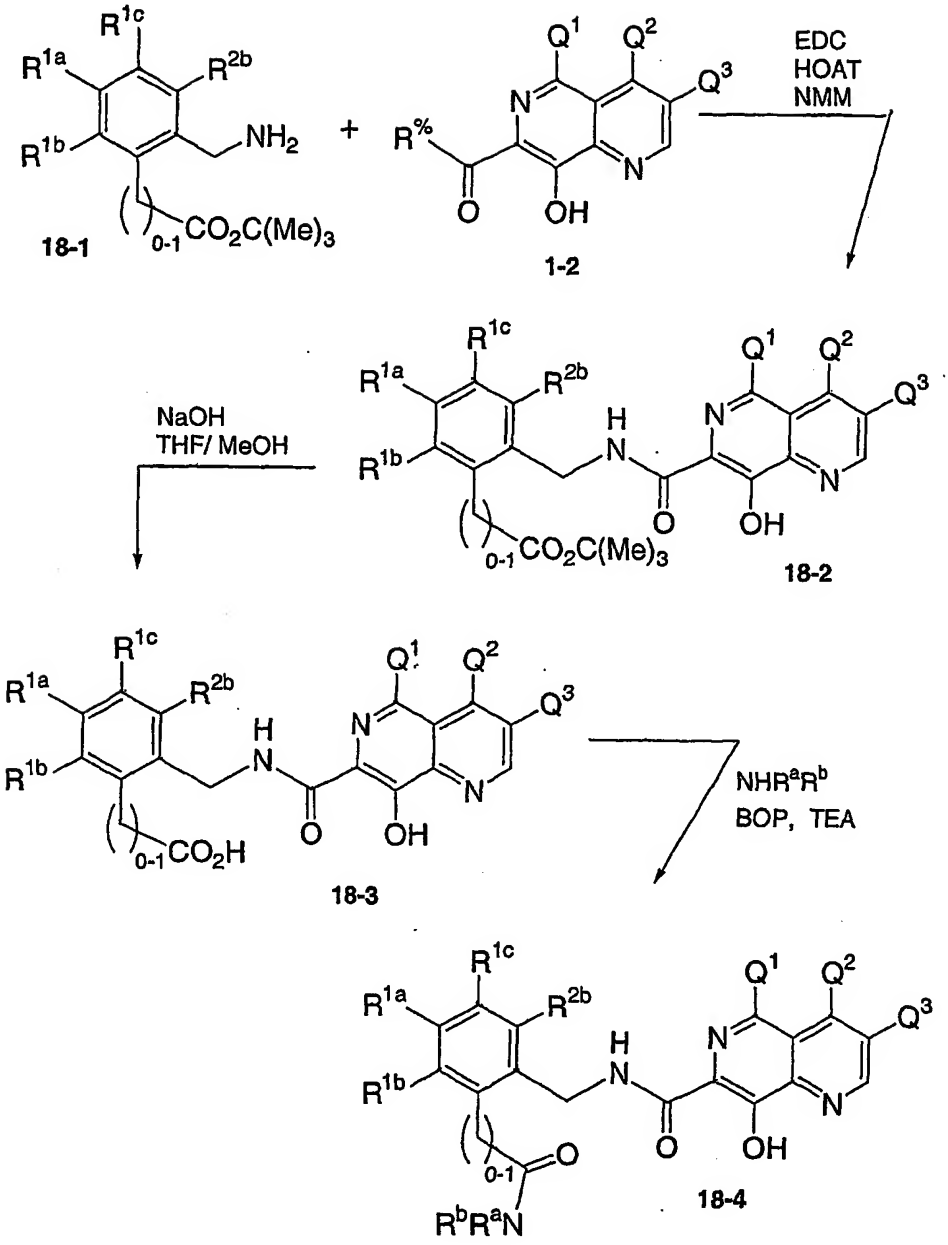
SCHEME 17





Scheme 18 shows a method for preparing compounds of the invention in which the benzylamine moiety has either an ortho-substituted amino-2-oxoethyl group or an ortho-substituted aminocarbonyl group. In this scheme, amine **18-1** is coupled with a suitable naphthyridine carboxylic acid under standard EDC /HOAt coupling conditions in the presence of a suitable base (e.g., NMM) to afford amide product **18-2**. The resulting ester can then be hydrolyzed to the acid which can then be coupled with a suitable amine.

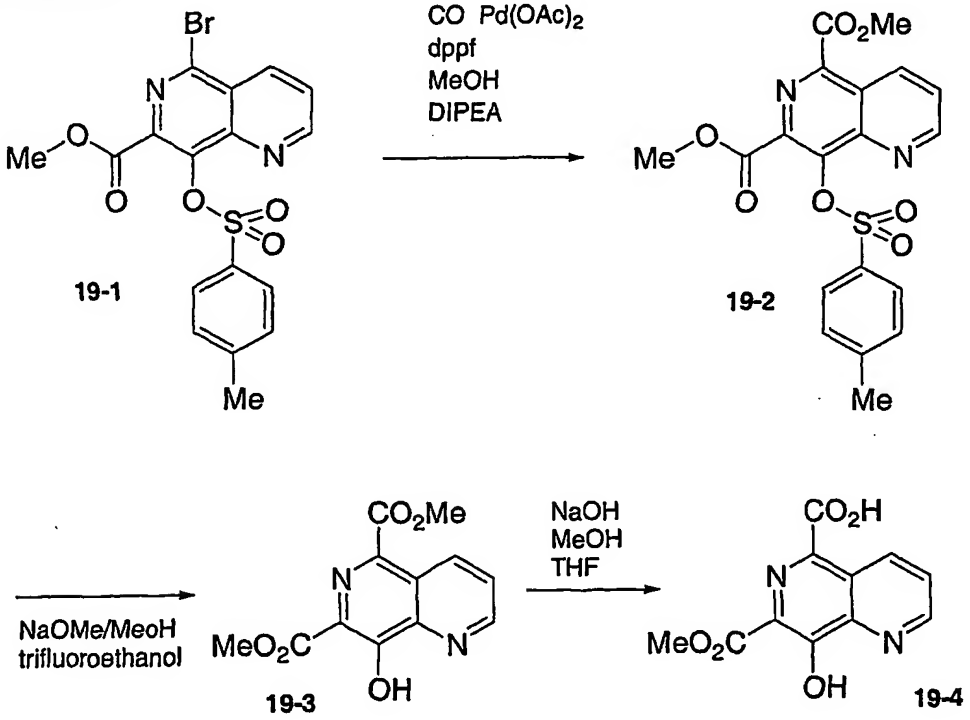
SCHEME 18

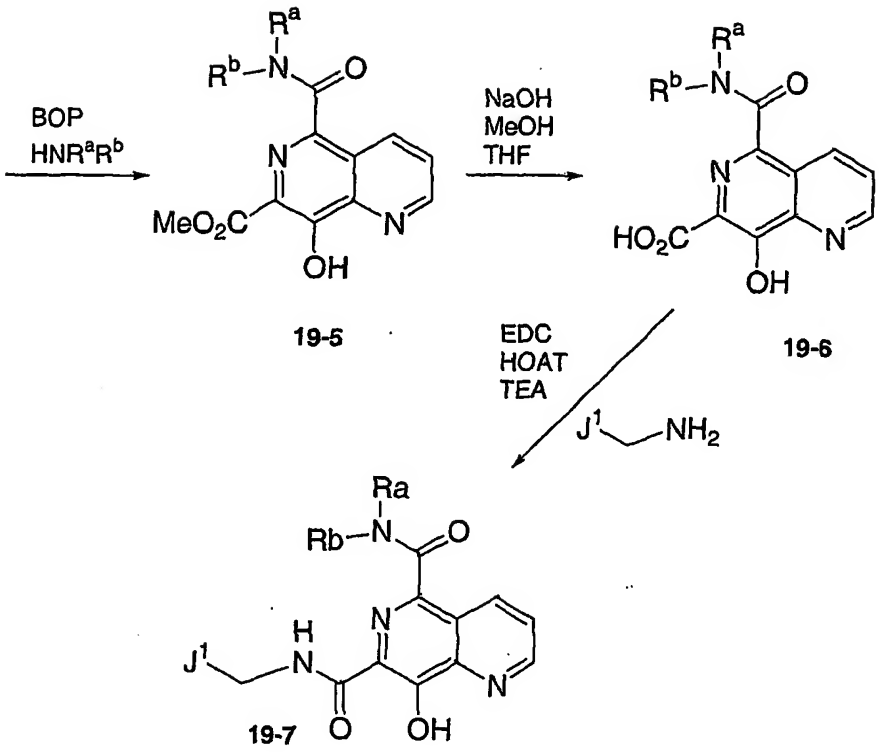


Scheme 19 describes the preparation of compounds having an aminocarboxy group at the 5-position of the naphthyridine ring. In this scheme, the brominated naphthyridine **19-1** is treated with carbon monoxide and methanol under

palladium catalysis utilizing 1,1"-bis(diphenylphosphino)ferrocene as a ligand, using conditions similar to those described in Ortar, *Tett. Letters* 1986, 27 (33): 3931, to afford acylated naphthyridine **19-2**. Removal of the tosyl protecting group with sodium methoxide in an alcholic solvent (e.g., trifluoroethanol) affords the dimethyl dicarboxylate **19-3**, which can be selectively hydrolyzed under aqueous base conditions (e.g., as described in Jerry March, Advanced Organic Chemistry, 3rd edition, John Wiley & Sons, 1985, pp. 334-338) to the carboxylic acid **19-4**. The amide **19-5** can then be obtained from **19-4** with conventional amide coupling reagents like BOP or EDC in the presence of excess amine. The 7-position ester can then be hydrolyzed with aqueous base to afford the acid **19-6**, which can then be coupled with a suitable benzylamine to give **19-7**.

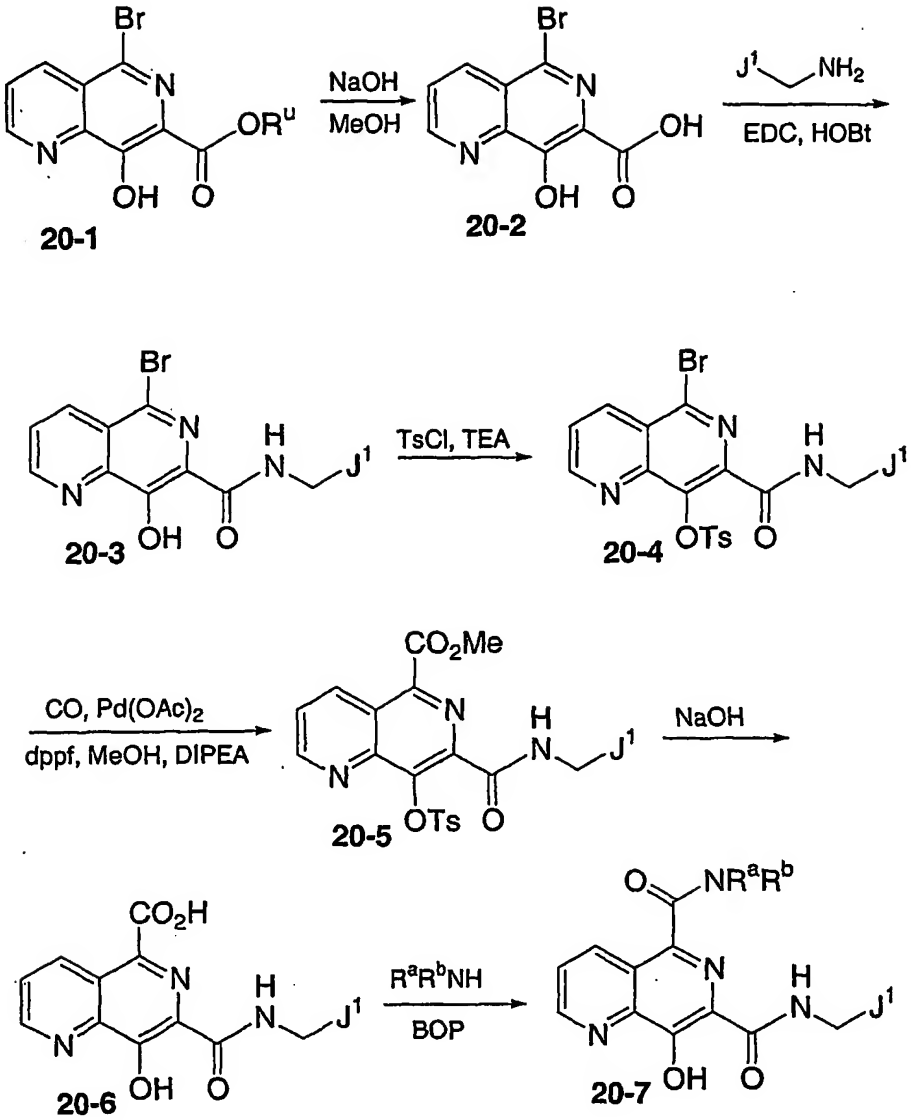
SCHEME 19





Compounds of the invention that comprise an amide substituent at the 5-position of the naphthyridine can also be prepared in the manner set forth in Scheme 20. The brominated naphthyridine ester **20-1** prepared as described in Scheme **17** can be hydrolyzed to the acid and coupled using standard reagents to an appropriately substituted amine to give **20-3**. Protection of the phenolic oxygen with a tosyl group under standard conditions gives the bromide **20-4**, which can the react with carbon monoxide and methanol under palladium catalysis as described for Scheme **19** to afford the ester **20-5**. This material can then be treated with base to remove the protecting group and elaborated under standard conditions to compounds of the invention **20-7**.

SCHEME 20



In the processes for preparing compounds and intermediates of the present invention as set forth in the foregoing schemes, functional groups in various moieties and substituents may be sensitive or reactive under the reaction conditions employed and/or in the presence of the reagents employed. Such sensitivity/reactivity can interfere with the progress of the desired reaction to reduce the yield of the desired product, or possibly even preclude its formation. Accordingly, it may be necessary or desirable to protect sensitive or reactive groups on any of the molecules concerned.

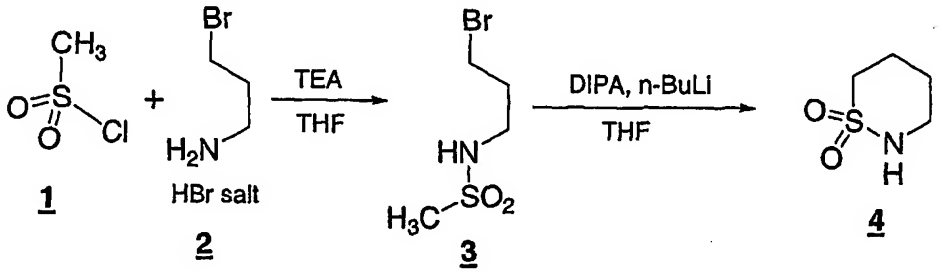
Protection can be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973 and in T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known in the art. Alternatively the interfering group can be introduced into the molecule subsequent to the reaction step of concern. For example, if one or more of the substituents R^{1a-c} and R^{2a-b} in amine **1-1** can interfere with the coupling reaction between reactants **1-1** and **1-2** of Scheme 1, the substituent can be incorporated into the molecule in a post-coupling step. Scheme 18 above illustrates the post-coupling introduction of an amide-containing substituent on the benzyl ring.

Further description of methods suitable for use (either directly or via routine modification) in preparing compounds of the present invention can be found in WO 02/30930 and in US _____, which is published U.S. Application Serial No. 09/973,853, filed October 10, 2001, the disclosure of which is incorporated herein by reference in its entirety.

The following examples serve only to illustrate the invention and its practice. The examples are not to be construed as limitations on the scope or spirit of the invention.

EXAMPLE 1

Preparation of 1,4-Butanesultam



	Weight	FW	Moles	Equiv.	Density	Volume
MsCl (1)	2.36 kg	114.55	20.6	1.03	1.480	1.59 L
3-bromopropyl-amine (2) HBr salt	4.40 kg	220	20.0	1.00		

TEA	4.07 kg	101.19	40.2	2.01	0.726	5.60 L
THF					43 + 4 + 8 = 55 L	
DIPA	481 g	101.19	4.75	0.25	0.722	666 mL
1,10-Phenanthroline	4.11 g	180.21				
n-BuLi, 1.6 M in hexane						

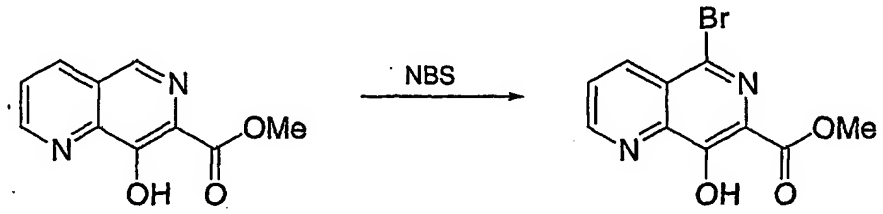
The 3-bromopropylamine-HBr salt (2) and THF (43 L) were placed in a 72 L round-bottomed-flask under N_2 and the resulting slurry was cooled to 0 °C. Two dropping funnels were fitted to the flask. One was charged with the TEA and the other with a solution of the MsCl (1) and THF (4 L). The contents of the addition funnels were added at roughly the same rate (the TEA was added slightly faster than the MsCl) while maintaining an internal reaction temperature below 10 °C. The addition required 2 h. The resulting white suspension was warmed to 23 °C and aged for 1 h. The suspended solids (a mixture of TEA-HBr and TEA-HCl) were removed by filtration through a dry frit. The cake was washed with THF (8 L). The combined filtrate and cake-rinse, a THF solution of 3, was collected in a 100 L round-bottomed-flask under N_2. To the solution of 3 was added the 1,10-phenanthroline and the DIPA and the resulting solution was cooled to -30 °C. The *n*-BuLi was added over about 4 h maintaining the internal temperature below -20 °C. After 1.25 eq of the *n*-BuLi was added the reaction mixture became deep brown and the color remained as the addition was completed. The reaction mixture was warmed to 0 °C over 3 h. A small aliquot was removed, and partitioned between saturated NH_4Cl and EtOAc. The EtOAc was evaporated and the residue examined by ^1H NMR to confirm consumption of 3 and conversion to 4. To the reaction mixture at 0 °C was added saturated aqueous NH_4Cl (12 L, the first 1L slowly, a heat kick to 6 °C was observed) and then brine (12 L). The phases were partitioned and the aqueous phase was extracted with EtOAc (20 L). The organic phases were combined, washed with brine (4 L) and then concentrated under vacuum to about 12 L. The solvent was switched to EtOAc (20 L used) maintaining a volume of 12 L. After the solvent switch, a yellow slurry resulted. *n*-Heptane (20 L) was added with stirring and the slurry was cooled to 5 °C. After a 1h age the solids were collected on a frit and rinsed with cold (5 °C) 3:5 EtOAc/*n*-

heptane. The wet cake was dried for 24 h under a stream of dry N_2 to provide 1.44 kg (53% from 2) of sultam 4 as a crystalline yellow solid.

EXAMPLE 2

Preparation of 5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxylic acid methyl ester

Step 1: 5-Bromo-8-hydroxy-1,6-naphthyridine-7-carboxylic acid methyl ester



5 [204.19] 6 [283.63]

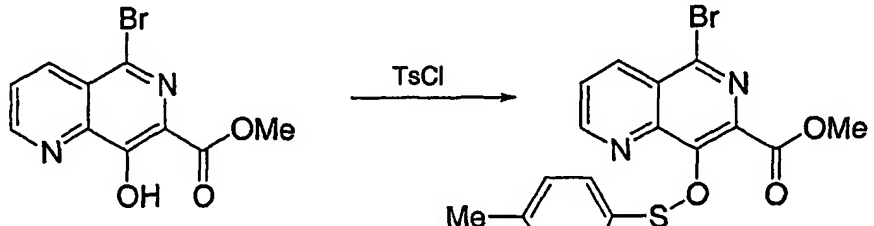
N-bromosuccinimide (7.83 g, 44.0 mmol) was added to a solution of 8-hydroxy-1,6-naphthyridine-7-carboxylic acid methyl ester (5, 8.17 g, 40.0 mmol) in chloroform (32 mL) over 20 min maintaining the temperature at 20-50 °C and the mixture was aged for 30 min at 50 °C. The mixture became a thick, stirrable slurry and HPLC analysis indicated <2% starting material remaining. The mixture was cooled to 30 °C over 15 min. MeOH (64 mL) was added over 30 min then a 1:1 mixture of MeOH-water (64 mL) was added over 30 min. The mixture was cooled to –40 °C over 30 min and aged at –40 °C for 30 min. The cold mixture was filtered and the solid was washed with 1:1 MeOH:water (100 mL) at 10-20 °C. The off white crystalline solid was dried under a stream of nitrogen to provide 10.48 g (93% yield) of 5-bromo-8-hydroxy-1,6-naphthyridine-7-carboxylic acid methyl ester (6).

HPLC retention times: 5 = 2.2 min, 6 = 6.0 min, HPLC conditions: 150 × 4.6 mm ACE 3 C18 column, isocratic elution with 30% MeCN in 0.025% aq H_3PO_4 at 1 mL/min, 25 °C with detection at 254 nm;

HPLC retention times: 5 = 1.8 min, 6 = 3.1 min, HPLC conditions: 150 × 4.6 mm ACE 3 C18 column, isocratic elution with 46% MeCN in 0.025% aq H_3PO_4 at 1 mL/min, 25 °C with detection at 254 nm.

^{13}C NMR of 6 ($CDCl_3$, 100 MHz): 169.7, 156.3, 154.5, 143.9, 137.1, 132.4, 128.0, 126.1, 124.2, 53.4.

Step 2: 5-Bromo-8-(4-toluenesulfonyloxy)-1,6-naphthyridin-7-carboxylic acid methyl ester



6
[283.63]

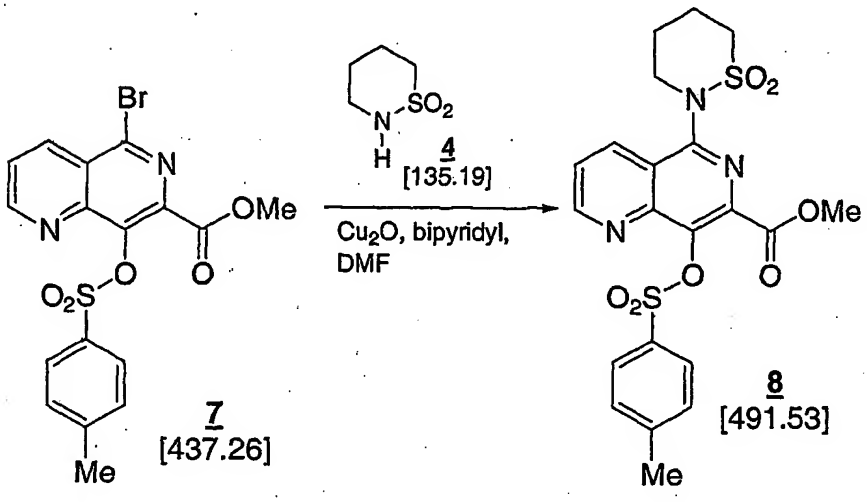
7
[437.26]

Triethylamine (0.759 g, 7.50 mmol) was added to a suspension of 5-bromo-8-hydroxy-1,6-naphthyridine-7-carboxylic acid methyl ester (6, 1.415 g, 5.000 mmol) in chloroform (5 mL) over 5 min maintaining the temperature at 20-50 °C to give a yellow suspension. *p*-Toluenesulfonyl chloride (1.15 g, 6.00 mmol) was added over 5 min maintaining the temperature at 20-40 °C to give a yellow solution. The mixture was aged at 40 °C for 2 h during which a crystalline solid precipitated out of the mixture and the color faded (HPLC analysis indicated <0.5% starting material remaining). The mixture was cooled to 20 °C over 15 min. MeOH (10 mL) was added over 30 min then a 1:1 mixture of MeOH:water (10 mL) was added over 30 min. The mixture was cooled to –40 °C over 30 min and aged at –40 °C for 30 min. The cold mixture was filtered and the solid was washed with 1:1 MeOH:water (10 mL), MeOH (5 mL), MTBE (10 mL) and hexanes (10 mL) all at 10-20 °C. The off-white crystalline solid was dried under a stream of nitrogen to provide 2.112 g (97% yield) of 5-bromo-8-(*p*-toluenesulfonyloxy)-1,6-naphthyridine-7-carboxylic acid methyl ester (7).

HPLC retention times: 6 = 3.1 min, 7 = 12.4 min; HPLC conditions: 150 × 4.6 mm ACE 3 C18 column, isocratic elution with 46% MeCN in 0.025% aq H_3PO_4 at 1 mL/min, 25 °C with detection at 254 nm.

^{13}C NMR of 7 (d6-DMSO, 100 MHz): 163.2, 157.0, 146.5, 145.8, 141.9, 141.3, 139.2, 137.2, 132.3, 130.4, 129.0, 127.6, 127.1, 53.3, 21.7.

Step 3: 5-(1,1-Dioxido-1,2-thiazinan-2-yl)-8-(4-toluenesulfonyloxy)-1,6-naphthyridine-7-carboxylic acid methyl ester.



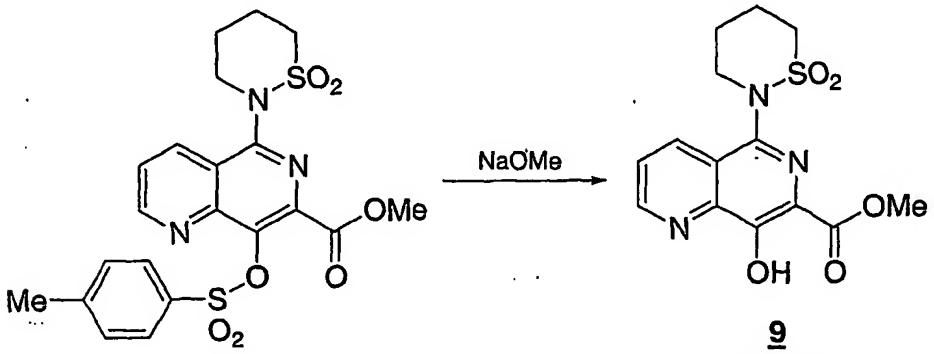
A mixture of 5-bromo-8-(*p*-toluenesulfonyloxy)-1,6-naphthyridine-7-carboxylic acid methyl ester (7, 2.186 g, 5.000 mmol), 1,4-butane sultam (4, 811 mg, 6.00 mmol), copper (I) oxide (858 mg, 6.00 mmol, <5 micron), 2,2'-bipyridyl (937 mg, 6.00 mmol) and DMF (10 mL) was degassed by stirring under a stream of nitrogen for 1 min and heated to 120 °C for 4 h. The brown suspension became a dark red solution with a small amount of undissolved copper (I) oxide remaining (HPLC analysis indicated <0.5% starting material remaining). The mixture was diluted with chloroform (10 mL), Solkaflok (200 mg) was added and the resulting mixture was filtered through a plug of Solkaflok. The plug was washed with chloroform (10 mL) and the combined filtrates were stirred vigorously with a solution of EDTA disodium salt dihydrate (3.8 g, 10.2 mmol) in water (40 mL) while air was slowly bubbled in for 40 min. The upper aqueous phase became turquoise while the lower organic phase became yellow. The organic phase was washed with a solution of EDTA disodium salt (1.9 g, 5.1 mmol) in water (30 mL) and a solution of sodium bisulfate monohydrate (0.87g, 6.3 mmol) in water (30 mL). Each of the above three aqueous phases was back extracted sequentially with one portion of chloroform (15 mL). The organic phases were dried over sodium sulfate and filtered. The dried organic extracts were concentrated and solvent switched to a final volume of 15 mL MeOH using a total of 30 mL MeOH for the switch at atmospheric pressure. Product crystallized during the solvent switch. The resulting slurry was cooled to 0 °C over

30 min and aged at 0 °C for 30 min. The slurry was filtered cold and the solid was washed with MeOH (15 mL). The off white solid was dried under a stream of nitrogen to provide 1.910 g (78%) of 5-(*N*-1,4-butanesultam)-8-(*p*-toluenesulfonyloxy)-1,6-naphthyridine-7-carboxylic acid methyl ester (8).

HPLC retention times: 7 = 12.4 min, 8 = 10.3 min, DMF = 1.3 min, Bipy = 1.5 min, HPLC conditions: 150 x 4.6 mm ACE 3 C18 column, isocratic elution with 46% MeCN in 0.025% aq H_3PO_4 at 1 mL/min, 25 °C with detection at 254 nm.

^{13}C NMR of 8 ($CDCl_3$, 100 MHz): 164.2, 155.3, 151.9, 146.7, 145.4, 141.2, 137.8, 135.3, 133.6, 129.6, 128.9, 125.4, 124.3, 53.4, 52.9, 48.7, 24.2, 22.0, 21.7.

Step 4: 5-(1,1-Dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxylic acid methyl ester



8
[491.53]

9
[337.35]

5-(*N*-1,4-butanesultam)-8-(*p*-toluenesulfonyloxy)-1,6-naphthyridine-7-carboxylic acid methyl ester (8, 1.597 g, 3.250 mmol) was dissolved in DMF (3.25 mL) at 40 °C and transferred to a solution of 0.5M NaOMe in MeOH (16.25 mL, 8.125 mmol) over ca 1-2 min at 20-25 °C. The resulting yellow homogenous mixture was heated to 50 °C and aged for 5 min (HPLC analysis indicated <0.5% starting material remaining). Mixture was cooled to 25 °C over 15 min and aged at 25 °C for 15 min during which a yellow crystalline precipitate was deposited. Acetic acid (390 mg, 6.50 mmol) was added over 1 min (yellow color faded) then water (32.5 mL) was added over 15 min at 25 °C. The slurry was aged for 30 min 25 °C and filtered. The filter cake was washed with 1:1 MeOH:water (32.5 mL) and then with 1:1 MTBE:hexanes (8 mL). The filter cake was dried under a stream of nitrogen to

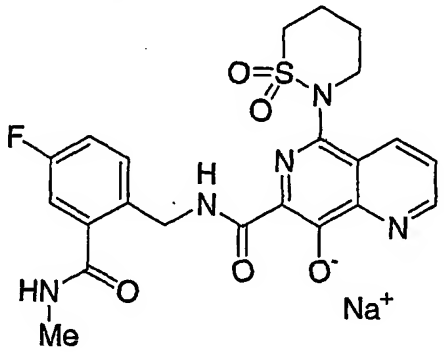
provide 1.064 g (97%) of 5-(*N*-1,4-butanesultam)-8-hydroxy-1,6-naphthyridine-7-carboxylic acid methyl ester (9) as an off white crystalline solid.

HPLC retention times: 8 = 10.3 min, 9 = 2.9 min, HPLC conditions: 150 x 4.6 mm ACE 3 C18 column, isocratic elution with 46% MeCN in 0.025% aq H_3PO_4 at 1 mL/min, 25 °C with detection at 254 nm.

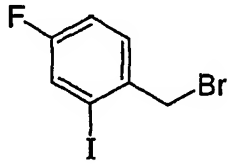
^{13}C NMR of 9 (d6-DMSO, 100 MHz): 167.8, 154.4, 153.5, 143.9, 143.7, 135.2, 125.9, 125.2, 124.4, 53.2, 53.1, 49.1, 24.4, 21.9.

EXAMPLE 3

Sodium 5-(1,1-dioxido-1,2-thiazinan-2-yl)-7-[({4-fluoro-2-[(methylamino)carbonyl]-benzyl}amino)carbonyl]-1,6-naphthyridin-8-olate



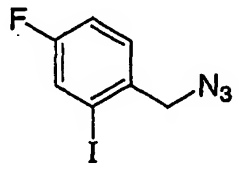
Step 1: 1-(Bromomethyl)-4-fluoro-2-iodobenzene



A suspension of 4-fluoro-2-iodotoluene (14.3 g, 60.6 mmol, Lancaster Synthesis), *N*-bromosuccinimide (16.2 g, 90.9 mmol), and benzoyl peroxide (0.74 g, 3.0 mmol) in carbon tetrachloride (500 mL) was heated to reflux for 3 days. Additional NBS (0.5 eq portions) was added as needed over this period to drive the reaction to completion. The reaction was cooled, filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (ISCO column, 110 g silica gel) eluting with 100% hexane to afford the desired product as a white solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 7.79 (1H, dt, J = 8.4, 1.3 Hz), 7.68 (1H, m), 7.31 (1H, m), and 4.74 (2H, s) ppm.

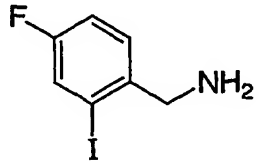
Step 2: 1-(Azidomethyl)-4-fluoro-2-iodobenzene



A suspension of 1-(bromomethyl)-4-fluoro-2-iodobenzene (15.68 g, 47.8 mmol) and sodium azide (4.21 g, 64.7 mmol) in dry DMF (30 mL) was heated to 50°C for six hours. The reaction was filtered and the filtrate was concentrated *in vacuo* to a volume of about 10 mL. The crude was purified by flash column chromatography (ISCO column, 110 g silica gel) eluting with 100% hexane to afford the desired product as a clear oil.

^{1}H NMR (DMSO-d6, 400 MHz) δ 7.83 (1H, dd, J = 8.3, 2.7 Hz), 7.54 (1H, dd, J = 8.6, 6.1 Hz), 7.33 (1H, td, J = 8.5, 2.6 Hz), and 4.52 (2H, s) ppm.

Step 3: 1-(4-Fluoro-2-iodophenyl)methanamine

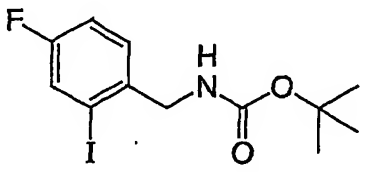


Triphenylphosphine (13.2 g, 50.4 mmol) was added to 1-(azidomethyl)-4-fluoro-2-iodobenzene (9.31 g, 33.6 mmol) dissolved in dry DMF (20 mL) at 0°C. After one hour water (3.03 mL, 168 mmol) was added and the solution was heated to 55°C for one hour. The reaction was cooled and the solution was concentrated to about 10 mL *in vacuo*. The residue was purified in two runs by preparative HPLC (Gilson semi preparative HPLC system using a Waters Delta pak column (3(10x40 mm I.D.) cartridges, C18, 15 μM pore size) eluting with 95-5% water (0.025% TFA) / acetonitrile (0.025% TFA) at 45 mL/min) to give the desired product in 75% purity. Using a Waters OASIS MCX Cartridge (6 g, 35 cc syringe), half of the 75% pure product dissolved in methanol was loaded onto the column pre-

equilibrated with a 1:1 solution of water and methanol. The column was washed once with the 1:1 solution and then washed several times with methanol to remove all UV active material. The amine was eluted by washing the column with methanol saturated with ammonia gas. This procedure was repeated on the remaining 75% pure product. The two batches were combined and concentrated *in vacuo* to give the free base of the desired product as a yellow oil.

^{1}H NMR (DMSO-d6, 400 MHz) δ 8.28 (2H, bs), 7.86 (1H, dd, J = 8.2, 2.7 Hz), 7.53 (1H, dd, J = 8.6, 5.9 Hz), 7.41 (1H, td, J = 8.5, 2.6 Hz), and 4.09 (2H, s) ppm.

Step 4: Tert-butyl 4-fluoro-2-iodobenzylcarbamate

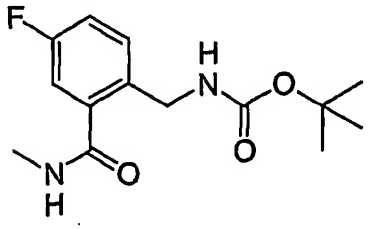


Triethylamine (1.41 mL, 10.1 mmol) was added to a 0°C suspension of 1-(4-fluoro-2-iodophenyl)methanamine (2.30 g, 9.16 mmol) and di-*tert*-butyl dicarbonate (2.20 g, 10.1 mmol) in dry methylene chloride (60 mL). The homogeneous solution was stirred at 0°C for five minutes then at room temperature for two hours. The reaction was diluted with methylene chloride (30 mL), washed with water three times and washed once with brine. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to a clear oil. The residue was purified by flash column chromatography (ISCO column, 110 g silica gel) eluting with a 10-25% ethyl acetate / hexane gradient over 30 minutes to afford the desired product as a clear oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.55 (1H, dd, J = 8.0, 2.5 Hz), 7.34 (1H, t, J = 7.1 Hz), 7.05 (1H, td, J = 8.3, 2.4 Hz), 5.02 (1H, m) 4.31 (2H, d, J = 6.0 Hz) and 1.46 (9H, s) ppm.

ES HRMS: calc'd for $C_{12}H_{15}FINO_2$+Na 374.0024, observed 374.0022.

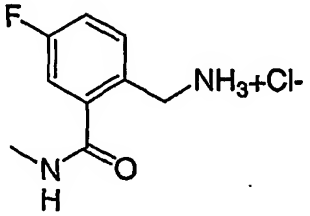
Step 5: Tert-butyl 4-fluoro-2-[(methylamino)carbonyl]benzylcarbamate



Through a solution of tert-butyl 4-fluoro-2-iodobenzylcarbamate (1.00 g, 2.85 mmol) in dry DMF (20 mL), in an oven dried glass insert in a high pressure bomb reactor flushed with nitrogen, was bubbled methylamine gas at 0°C until the solution was saturated and excess methylamine was condensed into the reaction (approximately 30 equivalents of methylamine). Diisopropylethylamine (0.99 mL, 5.70 mmol), palladium acetate (64 mg, 0.29 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (158 mg, 0.29 mmol) were added to the saturated solution. The glass insert was then placed in the pressure vessel and the vessel was purged once with carbon monoxide gas. The vessel was recharged with carbon monoxide gas to pressure of 300 psi, placed into an oil bath, and heated to 90°C for four hours. The vessel was cooled, the gas was released slowly and the resulting mixture was partitioned between water and ethyl acetate. The layers were separated and the organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to a brown liquid. The residue was purified by flash column chromatography (ISCO column, 110 g silica gel) eluting with a 10-50% acetone / hexane gradient over 35 minutes to afford the desired product as a brown crystalline solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 8.38 (1H, d, J = 4.0 Hz), 7.35-7.19 (4H, m), 4.20 (2H, d, J = 6.1 Hz), 2.75 (3H, d, J = 4.6 Hz) and 1.39 (9H, s) ppm.

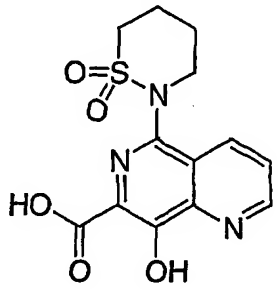
Step 6: {4-Fluoro-2-[(methylamino)carbonyl]phenyl}methanaminium chloride



Hydrogen chloride gas was bubbled through a –78°C solution of tert-butyl 4-fluoro-2-[(methylamino)carbonyl]benzylcarbamate (615mg, 2.18 mmol) in ethyl acetate (20 mL) until the solution was saturated. The flask was then allowed to warm to room temperature. The reaction was concentrated *in vacuo* to a volume of about 5 mL and the flask was capped and placed in the freezer overnight. In the morning, the solids that had precipitated were collected by vacuum filtration and washed with cold ethyl acetate to give the desired product as an off-white solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 8.81 (1H, d, J = 4.0 Hz), 8.25 (3H, bs), 7.62 (1H, dd, J = 8.3, 5.7 Hz), 7.50-7.42 (2H, m), 4.04 (2H, s), and 2.80 (3H, d, J = 3.7 Hz) ppm.

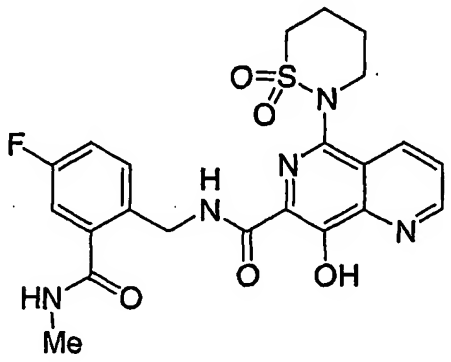
Step 7: 5-(1,1-Dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxylic acid



A suspension of methyl 5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxylate (1.00 g, 2.96 mmol, prepared as described in Example 2 above) in methanol (18 mL) with aqueous lithium hydroxide (17.8 mL, 17.8 mmol, 1N solution) was stirred overnight at 60°C. The suspension was acidified to a pH = 4 using 3N HCl (about 6 mL) and the resulting solution was allowed to stir overnight at room temperature. In the morning, the solids that had precipitated out of solution were collected by vacuum filtration to give the desired product as a light yellow solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 9.21 (1H, dd, J = 4.3, 1.6 Hz), 8.62 (1H, dd, J = 8.5, 1.6 Hz), 7.92 (1H, dd, J = 8.5, 4.3 Hz), 3.91-3.78 (2H, m), 3.55-3.45 (2H, m), 2.28 (3H, m) and 1.64 (1H, m) ppm.

Step 8: 5-(1,1-Dioxido-1,2-thiazinan-2-yl)-N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-8-hydroxy-1,6-naphthyridine-7-carboxamide



A solution of 5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxylic acid (100 mg, 0.31 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (89 mg, 0.46 mmol), 1-hydroxy-7-azabenzotriazole (63 mg, 0.46 mmol), {4-fluoro-2-[(methylamino)carbonyl]phenyl}-methanaminium chloride (101 mg, 0.46 mmol) and triethylamine (65 µL, 0.46 mmol) in dry DMF (2 mL) was stirred at room temperature overnight. In the morning, a couple drops of water were added and the reaction was filtered through a glass fiber filter. The filtrated was purified by preparative HPLC (Gilson semi preparative HPLC system using a Waters Nova pak column (10x40 mm I.D. cartridges, C18, 6 µM pore size) eluting with 95-5% water (0.025% TFA) / acetonitrile (0.025% TFA) at 35 mL/min) to give the product as a TFA salt. The crude solid was dissolved in $CHCl_3$ and washed with aqueous saturated ammonium chloride solution. The aqueous layer was back-extracted with $CHCl_3$ three times and the combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the desired product as a pale yellow solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 9.53 (1H, s), 9.19 (1H, s), 8.68 (1H, s), 8.58 (1H, d, J = 8.0 Hz), 7.89 (1H, d, J = 3.8 Hz), 7.53 (1H, m), 7.41-7.34 (2H, m), 4.64 (2H, d, J = 5.7 Hz), 3.92-3.47 (4H, m), 2.83 (3H, d, J = 3.8 Hz), 2.35 (3H, m), and 1.64 (1H, m) ppm.

The title compound of Step 8 was also obtained as follows:

A solution of 5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxylic acid (1.00 g, 3.09 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.77 g, 4.02 mmol), and 1-hydroxy-7-azabenzotriazole (0.55 g, 4.02 mmol) in degassed dry DMF (20 mL) was aged for 30 minutes to preform the activated ester. Triethylamine (0.47 mL, 3.40 mmol) and {4-fluoro-2-[(methylamino)carbonyl]phenyl}-methanaminium chloride (0.74 g, 3.40 mmol) were added and the reaction stirred for 30 minutes. The reaction was poured into water, the pH was adjusted to ~10 using 1N NaOH, and resulting solution was extracted several times with $CHCl_3$. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. The residue was partitioned between basic water (pH = 10 using 1N NaOH) and ether. The layers were separated and the aqueous layer was extracted twice more with ether. The aqueous layer was then acidified to pH = 4 using 1N HCl and extracted several times with $CHCl_3$. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to a brown oil. Methanol was added to the flask and the flask was sonicated for 5 minutes. Solids crashed out of the solution upon sonication and were collected by vacuum filtration to afford the title compound as a whitish solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 9.53 (1H, s), 9.19 (1H, s), 8.68 (1H, s), 8.58 (1H, d, J = 8.0 Hz), 7.89 (1H, d, J = 3.8 Hz), 7.53 (1H, m), 7.41-7.34 (2H, m), 4.64 (2H, d, J = 5.7 Hz), 3.92-3.47 (4H, m), 2.83 (3H, d, J = 3.8 Hz), 2.35 (3H, m), and 1.64 (1H, m) ppm.

Step 9: Sodium 5-(1,1-dioxido-1,2-thiazinan-2-yl)-7- [({4-fluoro-2-[(methylamino)carbonyl]benzyl}amino)carbonyl]-1,6-naphthyridin-8-olate

Sodium hydroxide (150 µL, 0.15 mmol, 1N solution) was added to a cloudy solution of 5-(1,1-dioxido-1,2-thiazinan-2-yl)-N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-8-hydroxy-1,6-naphthyridine-7-carboxamide (73 mg, 0.15 mmol) in a 2 mL mixture of acetone, acetonitrile and water. The homogeneous bright yellow solution was allowed to stir at room temperature for 30 minutes. The solvent was removed *in vacuo* and dried overnight on the high vac with gentle heating to give the desired product as a bright yellow solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 12.12 (1H, s), 8.78 (1H, m), 8.66 (1H, d, J = 4.6 Hz), 8.29 (1H, d, J = 6.8 Hz), 7.56 (1H, dd, J = 8.4, 4.2 Hz), 7.46 (1H, dd, J = 8.3, 5.6

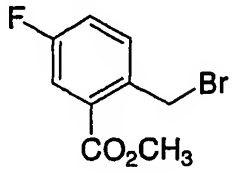
Hz), 7.26-7.19 (2H, m), 4.61 (2H, d, J = 5.9 Hz), 3.81 (2H, m), 3.51 (1H, m), 3.23 (1H, m), 2.81 (3H, d, J = 4.4 Hz), 2.43 (1H, m), 2.23 (2H, m) and 1.64 (1H, m) ppm.

ES HRMS: calc'd for $C_{22}H_{21}FN_5NaO_5S$ 510.1218, observed 510.1219.

EXAMPLE 3A

Preparation of {4-Fluoro-2-[(methylamino)carbonyl]phenyl}methanaminium chloride

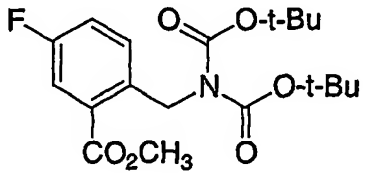
Step 1: Methyl 2-(bromomethyl)-5-fluorobenzoate



With no precautions to maintain a dry atmosphere, methyl 5-fluoro-2-methylbenzoate (Maybridge, 5g, 29.7 mmole) was dissolved in CCl_4 (50 mL). N-bromosuccinimide (5.82g, 32.7 mmol) and benzoyl peroxide (0.36g, 1.48 mmole) were added and the reaction brought to reflux overnight. An additional 0.3 eq of NBS and 0.01 eq of benzoyl peroxide was added and the reaction refluxed for 4 hrs, then cooled, filtered and concentrated. The residue was chromatographed on silica eluting with a gradient of 0-10% EtOAc/Hexanes. The fractions were collected to give the product, which was a mixture of mono and bis-brominated materials, as a clear oil.

^{1}H NMR ($CDCl_3$, 400 MHz, major product peaks) δ 7.67 (1H, dd, J= 2.8, 9 Hz), 7.45 (1H, dd, J = 5.4, 9 Hz), 7.20 (1H, m), 4.93 (2H, s), 3.95 (3H, s) ppm.

Step 2: Methyl 2-{[bis(*tert*-butoxycarbonyl)amino]methyl}-5-fluorobenzoate

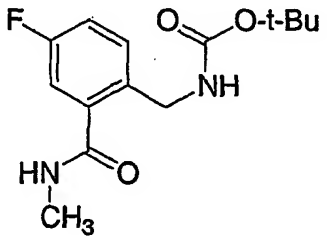


In a dry flask under nitrogen, di-tert-butyl iminodicarboxylate (Aldrich, 3.86g, 17.8 mmol) was dissolved in dry DMF (5 mL) and treated with NaH (60% dispersion in oil, 0.71g, 17.8 mmol). After the evolution of gas had ceased, Methyl 2-(bromomethyl)-5-fluorobenzoate (4g, 16.2 mmole) dissolved in DMF (5 mL) was

added. An additional 5 mL of DMF was added to aid stirring. The reaction was stirred for 2 hrs, then partitioned between water and EtOAc. The organic layer was dried with Na2SO4, filtered and concentrated and the residue was purified on silica eluting first with toluene, then with a gradient of 0-5% MeOH/CHCl3. The impure product thus obtained was re-chromatographed on silica eluting with a gradient of 0-30% EtOAc/Hexanes. The product was obtained as a clear oil.

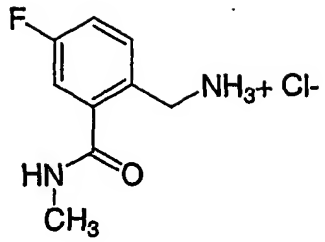
^{1}H NMR (DMSO, 400 MHz, major product peaks) δ 7.63 (1H, dd, *J*= 2.8, 9.4 Hz), 7.52 (1H, m), 7.20 (1H, dd, *J*= 5.3, 8.7 Hz), 4.98 (2H, s), 3.86 (3H, s), 1.38 (s, 18H) ppm.

Step 3: Preparation of tert-butyl 4-fluoro-2-[(methylamino)-carbonyl]benzylcarbamate



A solution of methyl 2-{[bis(*tert*-butoxycarbonyl)amino]methyl}-5-fluorobenzoate (5.0g, 13.04 mmol) in toluene (40 mL) was treated with methylamine gas at –78^{0}C until the solution was saturated. The reaction contents were then placed into a steel bomb and heated to 70^{0}C overnight. After cooling, the reaction was concentrated and then the solids were triturated with ether. The resulting solids were collected by vacuum filtration. As a result of the relatively harsh reaction conditions one of the t-butyloxycarbonyl protecting groups was removed from the molecule. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (1H, dd, *J* = 5.6, 8.3 Hz), 7.14-7.06 (2H, m), 6.64 (1H, BS), 5.69 (1H, BS), 4.26 (2H, d, *J* = 6.3 Hz), 2.98 (3H, d, *J* = 4.8 Hz), 1.41 (9H, s) ppm.

Step 4: Preparation of {4-fluoro-2-[(methylamino)carbonyl]phenyl}-methanaminium chloride



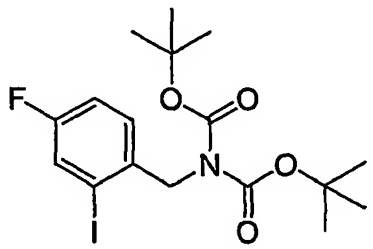
A solution of tert-butyl 4-fluoro-2-[(methylamino)carbonyl]-benzylcarbamate (2.59g, 9.17 mmol) in EtOAc (75 mL) was cooled to –78°C. After cooling solids precipitated out of the solution. HCl gas was added to the suspension until it reached saturation at which time the reaction became homogenous. After adding the HCl gas the dry ice bath was replaced with an ice water bath and the reaction was stirred for 10 minutes at 0°C. The solution was concentrated slowly and then redissolved in EtOAc and this was repeated two more times. The resulting solids were then triturated from EtOAc and fluffy white solids were collected by vacuum filtration.

^{1}H NMR (DMSO, 400 MHz) δ 8.82 (1H, d, J = 4.2 Hz), 8.34 (3H, bs), 7.64 (1H, dd, J = 5.6, 8.5 Hz), 7.49-7.41 (2H, m), 4.04 (2H, s), 2.80 (3H, d, J = 4.5 Hz) ppm.

EXAMPLE 3B

Alternative Preparation of {4-Fluoro-2-[(methylamino)carbonyl]phenyl}-methanaminium chloride

Step 1: Di(tert-butyl) 4-fluoro-2-iodobenzylimidodicarbonate

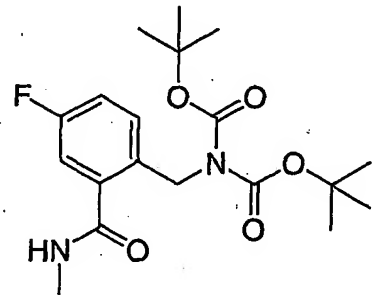


A solution of 1-(bromomethyl)-4-fluoro-2-iodobenzene (Example 3, step 1) (5g, 15.9 mmol) in dry DMF (50 mL) under argon was cooled to 2°C and treated with NaH (60% dispersion in oil, 0.4g, 17.5 mmol) and stirred for 5 minutes to give a fine slurry. A solution of di-tert-butyl iminodicarboxylate (Aldrich, 3.8g, 17.5 mmol) in 20ml dry DMF was added dropwise, keeping the temperature between 2 and

7°C. After stirring for 1 hr at 0°C, the solution was allowed to warm to room temperature and stirred overnight. The reaction was poured into bicarbonate solution and water was added until all the solids dissolved. The solution was extracted with ether and the combined organic layers were dried over Na_2SO_4, filtered and evaporated and the crude product was purified on 120g silica gel ISCO cartridge eluting first with a gradient of 0-5% EtOAc/Hexanes followed by a gradient of 5-10% EtOAc/Hexanes to give the product as a clear oil that solidified to a white solid.

^1H NMR ($CDCl_3$, 400 MHz) δ 7.55 (1H, bd, J = 7.3 Hz), 7.03 (2H, m), 4.72 (s, 2H), 1.44 (18H, s).

Step 2: Di(tert-butyl) 4-fluoro-2-[(methylamino)carbonyl]benzyl-imidodicarbonate



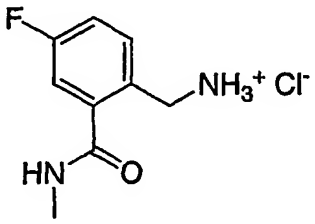
The glass reaction vessel from a Parr high pressure apparatus was briefly dried in an oven and di(tert-butyl) 4-fluoro-2-iodobenzylimidodicarbonate (5.17g, 11.5 mmol) was added and dissolved with stirring in 25 mL of dry DMF. Argon was bubbled through the solution while it was cooled to 0°C. Palladium acetate (0.064g, 0.29 mmol), DPPF (0.16g, 0.29 mmol), and diisopropylethylamine (3g, 23 mmol) were added, the flask was tared, and the solution was saturated with methylamine gas (10.5g methylamine, 338.6 mmol). The water condensed on the outside of the reaction vessel was wiped off and the vessel was placed in the Parr high pressure apparatus which was flushed with carbon monoxide gas, then sealed and pressurized to 75 psi carbon monoxide and heated to 70°C internal temperature for 4 hrs. The vessel was cooled and vented and the green solution was poured into water and extracted with ether. The combined ether layers were dried with Na2SO4, filtered and evaporated and the residue was chromatographed on a 120g ISCO silica gel cartridge eluting with a gradient of 25-30% EtOAc/Hexanes to give the product as a mixture of mono and bis-tert-butylimidocarbonate protected material that was taken

onto the next step. A small portion of the mono- and bis tert-butylimidocarbonate protected products were obtained pure and gave the following NMR.

^{1}H NMR ($CDCl_3$, 400 MHz) mono-protected product δ 7.42 (1H, dd, J = 5.6, 8.4 Hz), 7.1 (2H, m), 6.47 (1H, bs), 5.7 (1H, bs), 4.27 (2H, d, J = 6.4 Hz), 3.0 (3H, d, J = 4.9 Hz), 1.40 (9H, s) ppm.

^{1}H NMR (DMSO-d6, 400 MHz) bis-protected product δ 8.4 (1H, d, J = 4.3 Hz), 7.35-7.2 (2H, m), 7.11 (1H, dd, J = 5.5, 8.3 Hz), 4.81 (2H,s), 2.75 (3H, d, J = 4.5 Hz), 1.38 (18H, s).

Step 3: {4-fluoro-2-[(methylamino)carbonyl]phenyl)methanaminium chloride



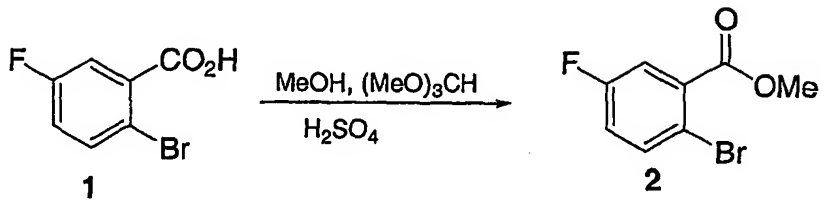
A mixture of mono and bis-protected intermediate from the previous step (4.58g, ~ 19 mmol) was dissolved in 200mL EtOAc and cooled to –60°C under argon. The solution was saturated with HCl gas then the flask was transferred to an ice bath and the reaction monitored by HPLC until no starting materials remained. The reaction vessel was placed on a rotoevaporator and the solvent removed carefully under vacuum, first with the flask out of the water bath, then with the flask in room temperature water bath, to give a white solid. This material was resuspended in EtOAc and the solvent removed again under vacuum. The residue was dried under high vacuum overnight, then suspended in ether and filtered to give the final product as a white solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 8.8 (1H, bs), 8.22 (3H, bs), 7.61 (1H, dd, J = 5.6, 8.4 Hz), 7.45 (2H, m), 4.04 (2H, s), 2.80 (3H, d, J = 4.5 Hz) ppm.

EXAMPLE 3C

Potassium 5-(1,1-dioxido-1,2-thiazinan-2-yl)-7-[({4-fluoro-2-[(methylamino)-carbonyl]benzyl}amino)carbonyl]-1,6-naphthyridin-8-olate

Step 1: Methyl 2-bromo-5-fluorobenzoate



1 2

Material	MW	Amount	Moles
2-bromo-5-fluorobenzoic acid	219.01	4.00 kg	18.3
methanol	32.04 (d = 0.791)	18 L	296.3
trimethylorthoformate	106.12	3.88 kg	36.5
96% sulfuric acid	98.08	0.373 kg	3.65
2M K_2HPO_4	174.18	4.82 L	9.68
ethyl acetate		16 L	
10% $NaHCO_3$	84.02	4 L	
25% brine		4 L	
toluene		12 L	
DMF			

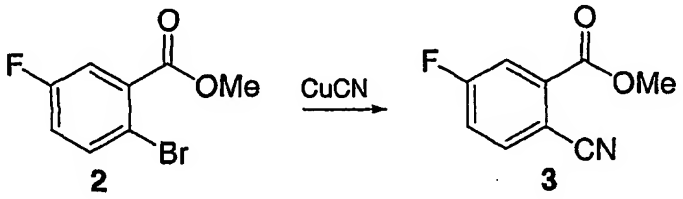
To a 72 L round bottom flask, equipped with an overhead stirrer, thermocouple, water-cooled condenser, and nitrogen inlet, was charged methanol (18 L). 2-Bromo-5-fluorobenzoic acid (4.00 kg), trimethyl orthoformate (3.876 kg), were then charged with stirring, followed by the addition 96% sulfuric acid (0.373 kg). The resulting solution was refluxed at 63 °C and aged for 10-16 hr, while the by-product (methyl formate) was removed during the reaction. The reaction mixture was monitored by HPLC. The reaction mixture was concentrated, then diluted with ethyl acetate (16 L), and cooled to 20 °C. 2 M potassium hydrogen phosphate (4.82 L) was then added to adjust the pH to 6.5-7. The mixture was then transferred to a 100 L nalgene extractor. After phase cut, the organic layer was washed with 10% $NaHCO_3$ (4 L), 25% brine (4 L), and then concentrated under reduced pressure. The residual oil was dissolved in toluene (6 L), and concentrated. This operation was done one

more time. The remaining oil was dissolved in DMF (total vol. 9.2 L). The resulting solution was used for next step.

HPLC conditions: column: Zorbax, Rx C8 250 x 4.6 mm; temperature: 30 ° C; detection: 210 nm; mobile phase: 0.1% aq H_3PO_4 (A)/MeCN (B); gradient: 90:10 (A)/(B) to 10:90 over 15 min, 10:90 hold for 5 min, 10:90 to 90:10 (A)/(B) over 10 seconds; flow rate: 1 mL/min; retention time for the desired monoester; 13.6 min.

Evaporation of a sample to dryness gave a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.64 (dd, J = 8.8, 5.0 Hz, 1H), 7.53 (dd, J = 8.8, 3.1 Hz, 1 H), 7.08 (td, J = 8.8, 3.1 Hz, 1 H), 3.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.4, 161.3 (d, J = 240.0 Hz), 135.9, 133.4, 120.0 (d, J = 20.0 Hz), 118.5 (d, J = 20.0 Hz), 116.1, 52.7.

Step 2: Methyl 2-nitrile-5-fluorobenzoate



2 3

Material	MW	Amount	Moles
methyl 2-bromo-5-fluorobenzoate	233.03		18.3 in DMF
copper(I) cyanide	89.56	1.60 kg	17.9
DMF		5 L + 4 L	
ethyl acetate		35 L + 17 L	
10% NH_4OH-20% NH_4Cl		37 L	
25% brine		8 L	
MeOH		33 L	

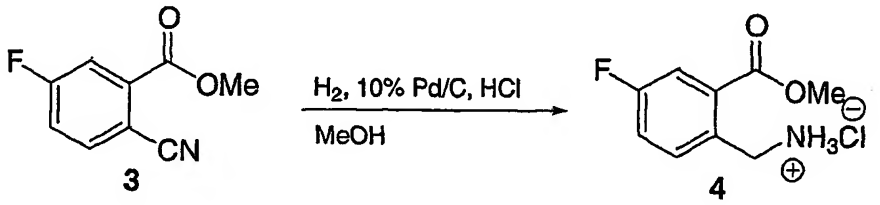
To a solution of methyl 2-bromo-5-fluorobenzoate (18.26 moles) in DMF (total vol. 9.2 L) was charged copper(I) cyanide (1.603 kg) in DMF (5 L) slurry and followed with a DMF flush (4 L). After being degassed, the reaction mixture was heated at 100 °C for 10-16 hours. The reaction mixture was monitored by HPLC. After being cooled to 50 °C-60 °C, ethyl acetate (20 L) was added, and then 10% NH_4OH-20% NH_4Cl (22 L). The mixture was then transferred to a 100 L nalgene

extractor. The 72 L round bottom flask was washed with 15 L of EtOAc and 15 L of water and transferred to the 100 L extractor. After phase cut, the aqueous layer was back-extraction with EtOAc (17 L) for one time. The combined organic layers were washed with 10% NH_4OH/20% NH_4Cl : water (1:1, 3 x 10 L), 16% brine (8 L), concentrated, and solvent switched to MeOH (total vol. 22 L, KF = 152.6 µg/mL). The resulting solution was used for next step.

HPLC conditions: column: Zorbax, Rx C8 250 x 4.6 mm; temperature: 30 ° C; detection at 210 nm; mobile phase: 0.1% aq H_3PO_4 (A)/MeCN (B); gradient: 90:10 (A)/(B) to 10:90 over 15 min, 10:90 hold for 5 min, 10:90 to 90:10 (A)/(B) over 10 seconds; flow rate: 1 mL/min; retention time for the desired monoester: 11.7 min.

Evaporation of a sample to dryness gave a light yellow solid: ^{1}H NMR ($CDCl_3$) δ: 7.86-7.80 (m, 2 H), 7.37 (td, J = 8.5, 2.6 H, 1 H), 4.02 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.3 (d, J = 260 Hz), 163.3, 137.1 (d, J = 10.0 Hz), 135.2 (d, J = 10.0 HZ), 120.2 (d, J = 30.0 Hz), 118.8 (d, J = 20.0 Hz), 116.6, 109.0, 53.1.

Step 3: Methyl 2-aminomethyl-5-fluorobenzoate, HCl salt



Material	MW	Amount	Moles
methyl 2-nitrile-5-fluorobenzoate	179.15		10.6 in MeOH
3.0 M HCl in MeOH (anhydrous)	36.46	7.10 L	21.22
10% Pd/C		0.475 kg	
solka floc		2.6 kg	
MeOH		3 x 10 L	

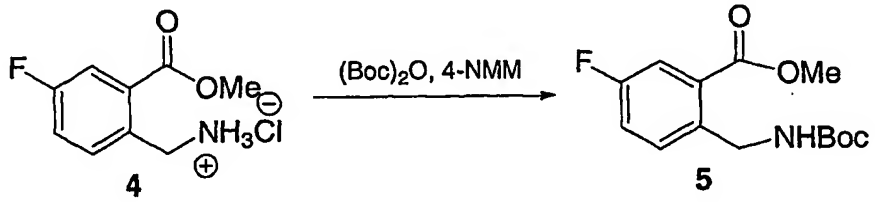
A degassed mixture of methyl 2-nitrile-5-fluorobenzoate (10.6 moles) in MeOH (total 10.0 L), 3.0 M HCl in MeOH (7.10 L), and 10% Pd/C (0.475 kg) was submitted to hydrogenation at 40 °C and 45 PSI for 48 hours. The reaction mixture was monitored by HPLC. After being cooled to ambient temperature, the reaction

mixture was then filtered by passing a short Solka Flock (2.6 kg), which was washed with MeOH (3 x 10 L). The combined filtrates were concentrated and solvent-switched to toluene in total volume (about 18 L, KF = 154 μg/mL). The crystalline solid was filtered off and washed with toluene, dried under vacuum with nitrogen sweep to afford the title compound (>99A% purity, HPLC).

HPLC conditions: column: Zorbax, Rx C8 250 x 4.6 mm; temperature: 30 ° C; detection at 210 nm; mobile phase: 0.1% aq H_3PO_4 (A)/MeCN (B); gradient: 90:10 (A)/(B) to 10:90 over 15 min, 10:90 hold for 5 min, 10:90 to 90:10 (A)/(B) over 10 seconds; flow rate: 1 mL/min; retention time for the desired monoester: 5.78 min.

^{1}H NMR ($CDCl_3$) δ: 8.43 (brs, 3 H), 7.74-7.65 (m, 2H), 7.55 (td, J = 8.4, 2.8 Hz, 1 H), 4.26 (q, J = 5.5 Hz), 3.85 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.8, 162.1 (d, J = 250 Hz), 134.8 (d, J = 10.0 Hz), 131.9 (d, J = 10.0 Hz), 131.7, 120.1 (d, J = 20.0 Hz), 117.7 (d, J = 30.0 Hz), 53.2, 40.3.

Step 4: Methyl 2-t-butyloxycarbonylaminomethyl-5-fluorobenzoate



4 5

Material	MW	Amount	Moles
ammonium salt 4	219.64	3.42 kg	15.6
$(Boc)_2O$	218.25	3.73 kg	17.1
NMM	101.15 (d = 0.920)	1.73 kg	17.1
40 wt.% $MeNH_2$	31.06	1.21 kg	15.6
toluene		31 L	
0.1 M EDTA Na sol'n		6.2 L	
25% brine		6.2 L	

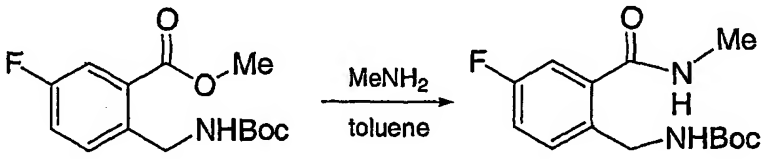
To the ammonium salt 4 (3.42 kg) in toluene (31L) was added $(Boc)_2O$ (3.73 kg), followed by NMM (1.73 kg), at 15°C- 20 °C over 1 hour. The reaction mixture was aged at room temperature for 15-24 hours, followed by the addition of 40 wt% methylamine aqueous (1.21 kg) at 5 °C-10 °C, after which the mixture was aged

at the same temperature for 2 hours to quench the excess $(Boc)_2O$. The reaction mixture was then worked up by charging water (12 L). After phase cut, the organic layer was washed with 0.1 M EDTA sodium solution (6.2 L), 25% brine (6.2 L), and concentrated to total volume (20 L), which was divided by two equal amount portions for amidation in two batches.

HPLC conditions: column: Zorbax, Rx C8 250 x 4.6 mm; temperature: 30 °C; detection at 210 nm; mobile phase: 0.1% aq H_3PO_4 (A)/MeCN (B); gradient: 90:10 (A)/(B) to 10:90 over 15 min, 10:90 hold for 5 min, 10:90 to 90:10 (A)/(B) over 10 seconds; flow rate: 1 mL/min; retention time for the desired monoester: 14.5 min.

Evaporation of a sample to dryness gave a colorless oil: ^1H NMR ($CDCl_3$) δ: 7.65 (dd, J = 9.4, 2.4, 1 H), 7.50 (dd, J = 8.0, 5.7 Hz, 1 H), 7.18 (dd, J = 8.0, 2.8 Hz, 1 H), 5.31 (brs, 1 H), 4.47 (d, J = 6.6 Hz, 1 H), 3.91 (s, 3 H), 1.41 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.5, 1.61.5 (d, J = 250 Hz), 155.8, 137.0, 132.8 (d, J = 10.0 Hz), 130.2 (d, J = 10.0 Hz), 119.6 (d, J = 30.0 Hz), 117.7 (d, J = 20.0 Hz), 79.2, 52.4, 42.9, 28.4 (3C).

Step 5: N-methyl 2-t-butyloxycarbonylaminomethyl-5-fluorobenzenecarboxamide



5 6

Material	MW	Amount	Moles
methyl benzoate **5**	283.30		7.77 in toluene
methylamine	31.06	0.483 kg	15.6
toluene		5 L	
heptane		50 L + 25 L	

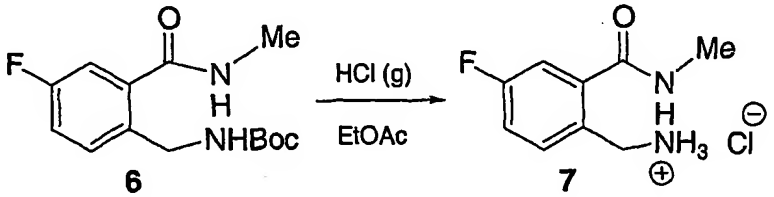
The crude methyl benzoate **5** in toluene (7.77 moles in 10 L) was cooled to -20 °C and methylamine (0.483 kg) gas was added. The mixture was then heated in an autoclave at 80-85 °C for 48 hours. The reaction was monitored by HPLC. After cooling to about 50 °C, the reaction mixture was transferred to a large round bottom flask for batch concentration. The solution was concentrated,

producing a slurry, and solvent-switched to toluene (total vol. 12 L), after which heptane (50 L) was slowly charged to the slurry. The resulting slurry was aged at 0 °C for 1 hour. The white crystalline solid was filtered off, rinsed with heptane (25 L), and dried under vacuum with a nitrogen sweep to give methylamide.

HPLC conditions: column: Zorbax, Rx C8 250 x 4.6 mm; temperature: 30 ° C; detection at 210 nm; mobile phase: 0.1% aq H_3PO_4 (A)/MeCN (B); gradient: 90:10 (A)/(B) to 10:90 over 15 min, 10:90 hold for 5 min, 10:90 to 90:10 (A)/(B) over 10 seconds; flow rate: 1 mL/min; retention time for the desired monoester: 11.6 min.

^{1}H NMR ($CDCl_3$) δ: 7.43 (dd, J = 8.4, 5.5 Hz, 1 H), 7.15-7.07 (m, 2 H), 6.52 (brs, 1 H), 5.66 (brs, 1 H), 4.28 (d, J = 6.4 Hz, 2 H), 3.10 (d, J = 4.8 H, 3 H), 1.42 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.0, 161.5 (d, J = 250 Hz), 156.1, 137.3, 133.5, 132.0 (d, J = 10.0 Hz), 117.2 (, d, J = 20.0 Hz), 114.3 (d, J = 20.0 Hz), 79.4, 42.2, 26.7.

Step 6: N-methyl 2-amino-5-fluorobenzenecarboxamide, HCl salt



6 7

Material	MW	Amount	Moles
N-methyl amide **6**	282.31	3.14 kg	11.1
HCl (gas)	36.46	3.25 kg	89.0
EtOAc		21.4 L + 42.8 L + 30 L	
heptane		40 L	

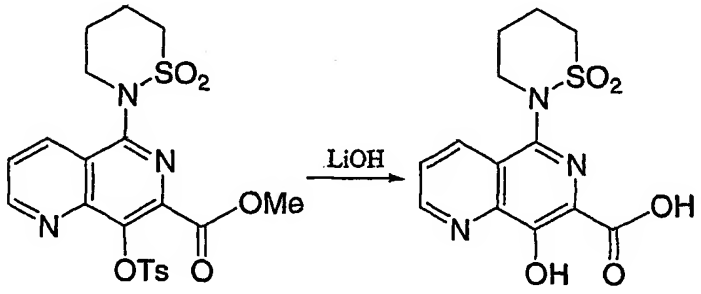
To a solution of ethyl acetate (21.4 L) was bubbled HCl gas (3.25 kg) at -20 °C. *N*-Methyl amide **6** (3.14 kg) was charged to the HCl-EtOAc solution, and the reaction mixture was warmed to ambient temperature (17 °C) in about 3 hours and aged for 2-4 hours. The reaction was monitored by HPLC. The reaction mixture was diluted with EtOAc (42.8 L), and the resulting slurry was aged at 0-5 °C for 0.5 hour. The crystalline solid was filtered off and washed with EtOAc (30 L), then with heptane (40 L), and then dried under vacuum with a nitrogen sweep to give the salt.

The crystalline solid (2.434 kg) was recrystallized by dissolved in methanol (10.5 L) at 30 °C. To the resulting solution was added EtOAc (64 L), producing a slurry that was aged at 0-5 °C for 1 hour. The white crystalline solid was filtered off and washed with EtOAc (30 L), dried under vacuum with nitrogen sweep to give the desired product.

HPLC conditions: column: Zorbax, Rx C8 250 x 4.6 mm; temperature: 30 ° C; detection at 210 nm; mobile phase: 0.1% aq H_3PO_4 (A)/MeCN (B); Gradient: 90:10 (A)/(B) to 10:90 over 15 min, 10:90 hold for 5 min, 10:90 to 90:10 (A)/(B) over 10 seconds; flow rate: 1 mL/min; retention time for the desired monoester: 3.33 min.

^{1}H NMR ($CDCl_3$) δ: 8.84 (brs, 1 H), 8.05 (brs, 3 H), 7.55 (dd, J = 8.3, 5.8 Hz, 1 H), 7.46-7.13 (m, 2 H), 4.01 (s, 3 H), 2.77 (d, J = 4.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.9, 162.0 (d, J = 250 Hz), 157.9, 138.5 (d, J = 10.0 Hz), 134.3 (d, J = 10.0 Hz), 129.2, 117.6 (d, J = 20.0 Hz), 115.5 (d, J = 20.0 Hz), 40.7, 26.7.

Step 7: 5-(1,1-Dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxylic acid

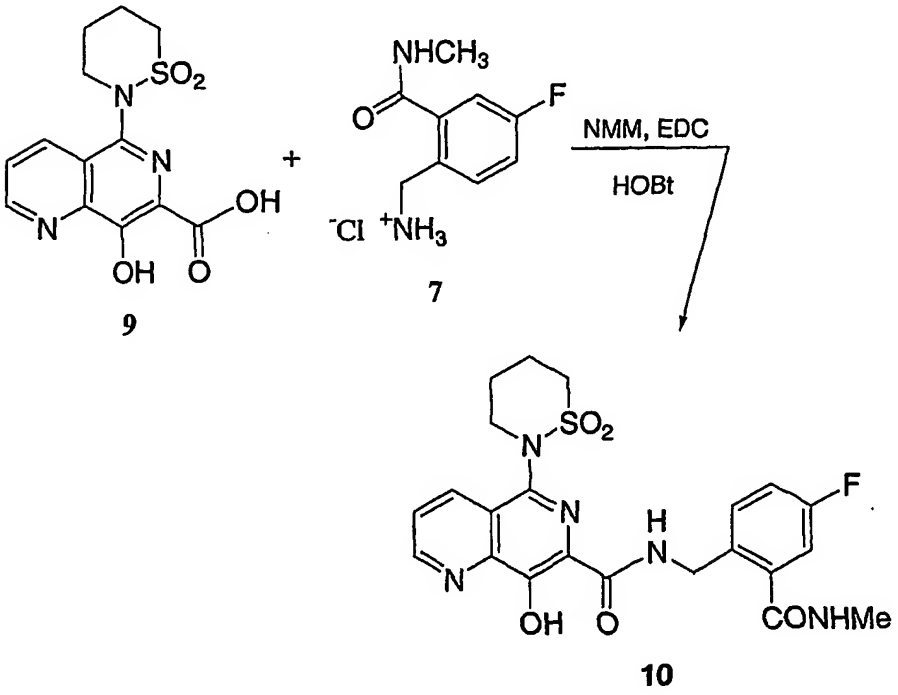


8 **9**

Material	MW	Equivalents	Amount	Moles
Tosylate **8**	491.5	1.0	3.3 kg	6.7
2-propanol		4 L/kg **8**	13.2 L	
water		4 L/kg **8**	13.2 L	
$LiOH \cdot H_2O$	41.96	3.3	0.93	22.2
2N HCl		2.6	8.7 L	17.5
Water		5 L/kg **8**	4 x 4.3 L	

A 50-L flask equipped with a mechanical stirrer, temperature probe, addition funnel, and nitrogen inlet was charged with 2-propanol (13.2 L) and tosylate **8** (3.3 kg). The lithium hydroxide monohydrate (0.93 kg) was then charged as a solution in GMP water (13.2 L) at 20-25 °C. The resulting suspension was warmed to 60 °C where a homogeneous yellow solution was obtained. The reaction was aged until complete conversion to **9** was reached as determined by HPLC assay (4-16 hours). The resulting yellow suspension was cooled to about 20 °C and diluted with 2 N HCl (8.7 L) over 0.5 hour. The pH was between 1.3-1.6 at 20 °C following HCl addition. The suspension was cooled to about 20 °C, filtered, and the cake was washed with water (4 x 4.3 L) as displacement washes. The cake was dried on the filter pot under nitrogen and house vacuum until the water content was <6 wt % by Karl Fisher titration. The purity of carboxylic acid phenol **9** was >99.4 A% by HPLC assay.

Step 8: 5-(1,1-Dioxido-1,2-thiazinan-2-yl)-N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-8-hydroxy-1,6-naphthyridine-7-carboxamide

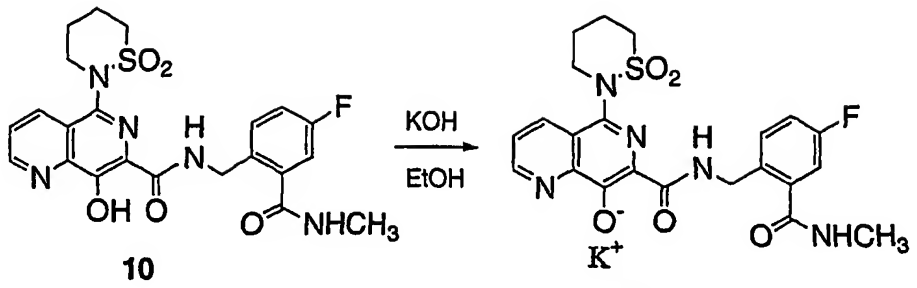


9 **7** **10**

Material	MW	Equivalents	Amount	Moles
carboxylic acid **9**	323.33	1.0	1.63 kg	5.04
DMF		10 L/kg **9**	16.3 L	
amine **7**	218.66	1.2	1.32 kg	6.05
HOBt	135.13	0.5	341 g	2.52
NMM	101.15	0.9	456 g	4.54
EDC • HCl	191.71	1.5	1.45 kg	7.56
water		10 L/kg **9**	16.3 L	

A 50-L flask equipped with a mechanical stirrer, temperature probe, and nitrogen inlet was charged with the dry DMF (16.3 L), carboxylic acid **9** (1.73 kg gross, 1.63 assay kg, KF = 6.0 wt % water), anhydrous HOBt (341 g), amine **7** (1.32 kg), and NMM (456 g, 500 mL). The suspension was agitated at 20 °C until a homogeneous solution was obtained and then cooled to 0-5 °C. The EDC (1.45 kg) was added and the reaction aged until complete conversion of **9** was reached as determined by HPLC (<0.5% **9**, about 16 hours). The reaction was diluted with water (1.6 L) at 20 °C, seeded (11 g), and aged for 0.5 hour. The batch was diluted with water (14.7 L) to give a 1:1 v/v ratio of water:DMF and then cooled to 0 °C. The batch was then filtered and the cake washed with chilled 1:1 water:DMF (4 x 2.5 L) and chilled water (4 x 5.5 L) as displacement washes. The cake was then dried at ambient temperature under nitrogen tent/house vacuum to obtain the title product (purity: >99.0 A% by HPLC assay).

Step 9: Potassium 5-(1,1-dioxido-1,2-thiazinan-2-yl)-7- [({4-fluoro-2-[(methylamino)carbonyl]benzyl}amino)carbonyl]-1,6-naphthyridin-8-olate



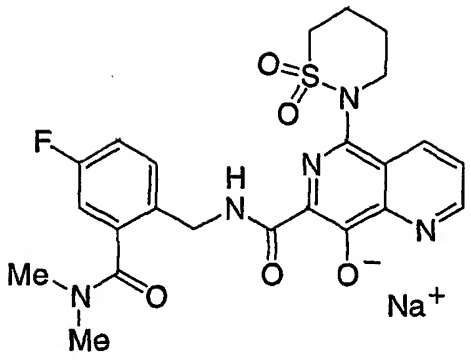
10 11

Material	MW	Equivalents	Amount	Moles
carboxamide **10**	487.1	1.0	4.2 kg	8.61
EtOH			20 mL/g **10**	
KOH (45 wt.% aq)	56.1	1.2	1286 g (866 mL)	10.34

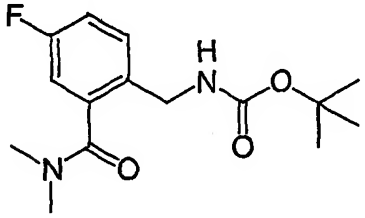
A 100 L cylinder equipped with a mechanical stirrer, temperature probe, addition funnel, and nitrogen inlet was charged with carboxamide **10** and EtOH (84 L) and then heated to 60 °C. To the resulting yellow suspension was added aq KOH . The resulting yellow solution was filtered through a 10 μm line filter into an adjacent 100 L flask. The solution was seeded and heated at 60 °C for 3 hours and then allowed to cool to room temperature overnight. The resulting slurry was cooled to 3-4 °C, filtered, and washed with 4 X 2 L of cold EtOH. The filter pot was placed under vacuum with a N_2 stream to obtain the title salt as a crystalline ethanolate salt. The purity of the salt was >99.6 A% by HPLC assay. The salt contained 6.8 wt. % ethanol by GC and 0.5 wt. % water by Karl Fisher titration.

EXAMPLE 4

Sodium 7-[({2-[(dimethylamino)carbonyl]-4-fluorobenzyl}amino)carbonyl]-5-(1,1-dioxido-1,2-thiazinan-2-yl)-1,6-naphthyridin-8-olate

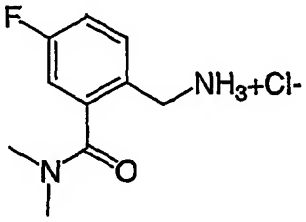


Step 1: tert-butyl 2-[(dimethylamino)carbonyl]-4-fluorobenzylcarbamate



This compound was prepared in a manner similar to that described in Example 3, using dimethylamine instead of methylamine, to afford a light brown oil. ^{1}H NMR (DMSO, 400 MHz) δ 7.36 (3H, m), 7.08 (1H, dd, J = 8.8, 2.6 Hz), 4.02 (2H, m), 2.99 (3H, s), 2.76 (3H, s) and 1.39 (9H, s) ppm.

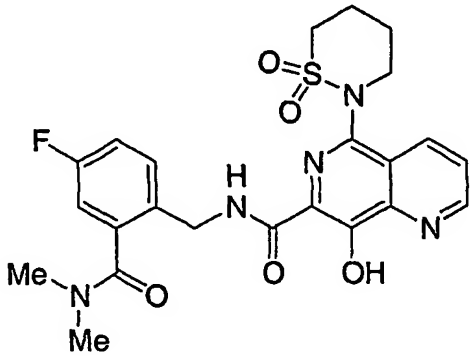
Step 2: {2-[(dimethylamino)carbonyl]-4-fluorophenyl}methanaminium chloride



This compound was prepared in a manner similar to that described in Example 3 to afford a light pink solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 8.38 (2H, bs), 7.69 (1H, dd, J = 8.4, 5.5 Hz), 7.39 (1H, dt, J = 8.5, 1.8 Hz), 7.33 (1H, dd, J = 9.0, 1.8 Hz), 3.91 (2H, s), 3.03 (3H, s), and 2.86 (3H, s) ppm.

Step 3: N-{2-[(Dimethylamino)carbonyl]-4-fluorobenzyl}-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide



In a similar manner as described for Example 3, the title compound was prepared as a light yellow solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 9.17 (2H, m), 8.45 (1H, m), 7.87 (1H, m), 7.52 (1H, m), 7.26 (2H, m), 4.54 (2H, m), 3.84 (2H, m), 3.65 (1H, m), 3.48 (1H, m), 3.02 (3H, s), 2.85 (3H, s), 2.30 (3H, m), and 1.66 (1H, m) ppm.

Step 4: Sodium 7-[({2-[(dimethylamino)carbonyl]-4-fluorobenzyl}amino)-carbonyl]-5-(1,1-dioxido-1,2-thiazinan-2-yl)-1,6-naphthyridin-8-olate

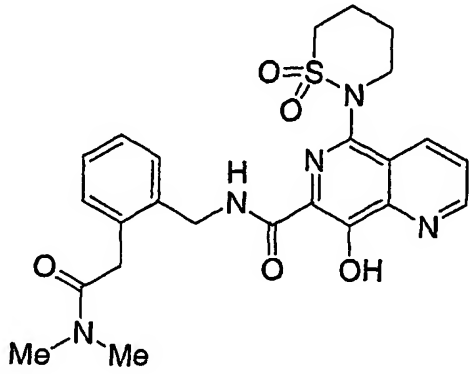
In a similar manner as described for Example 3, the title compound was prepared as a yellow solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 12.05 (1H, bs), 8.78 (1H, m), 8.28 (1H, d, J = 8.2 Hz), 7.55 (1H, dd, J = 8.2, 4.3 Hz), 7.48 (1H, m), 7.21 (1H, m), 7.09 (1H, m), 4.49 (2H, m), 3.83 (3H, m), 3.44 (2H, m), 3.01 (3H, s), 2.78 (3H, s), 2.24 (2H, m), and 1.51 (1H, m) ppm.

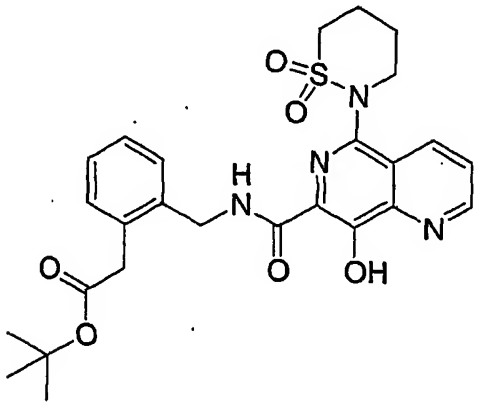
ES HRMS: calc'd for $C_{23}H_{24}FN_5O_5S$ + H: 502.1555, observed 502.1557.

EXAMPLE 5

N-{2-[2-(Dimethylamino)-2-oxoethyl]benzyl}-5- (1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide



Step 1: Tert-butyl {2-[({[5-(1,1-dioxido-1,2-thiazinan-2-yl)-8- hydroxy-1,6-naphthyridin-7-yl]carbonyl}amino)methyl]phenyl}acetate

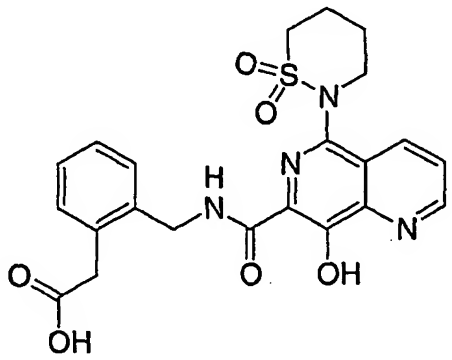


A solution of 5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxylic acid (75 mg, 0.23 mmol, prepared as described in Example 3), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (49 mg, 0.70 mmol), 1-hydroxy-7-azabenzotriazole (35 mg, 0.26 mmol), tert-butyl [2-(aminomethyl)phenyl]acetate oxalate (217 mg, 0.70 mmol, Prosynth Limited) and *N*-methylmorpholine (76 μL, 0.70 mmol) in dry DMF (0.5 mL) was stirred at room temperature for one hour. The reaction was filtered through a glass fiber filter and the filtrate was purified by preparative HPLC (Gilson semi preparative HPLC system using a Waters Nova pak column (10x40 mm I.D. cartridges, C18, 6 μM pore size)

eluting with 95-5% water (0.025% TFA) / acetonitrile (0.025% TFA) at 35 mL/min) to give the product as a bright yellow sticky solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 9.19(1H, m), 9.10 (1H, m), 8.64 (1H, m), 7.89 (1H, dd, J = 8.4, 4.2 Hz), 7.37 (1H, m), 7.27 (3H, m), 4.65 (2H, m), 4.41 (1H, m), 3.91 (1H, m), 3.80 (2H, s), 3.54 (2H, m), 2.25 (3H, m), 1.74 (1H, m) and 1.41 (9H, d, J = 1.3 Hz) ppm.

Step 2: {2-[({[5-(1,1-Dioxido-1,2-thiazinan-2-yl)-8-hydroxy- 1,6-naphthyridin-7-yl]carbonyl}amino)methyl]phenyl}acetic acid



Sodium hydroxide (0.81mL, 0.81 mmol, 1N solution) was added to tert-butyl {2-[({[5-(1,1-dioxido-1,2-thiazinan-2-yl)-8- hydroxy-1,6-naphthyridin-7-yl]carbonyl}amino)methyl]phenyl}acetate (85 mg, 0.16 mmol) dissolved in a 1:1 solution of THF/methanol (2 mL) and heated for three hours at 50°C. More sodium hydroxide solution (0.81mL, 0.81 mmol, 1N solution) was added and the solution was stirred overnight at 50°C. In the morning, the reaction was cooled and acidified to a pH = 4 using 1N HCl solution (~1.6 mL). The solids that crashed out of solution were isolated by vacuum filtration to give the desired product as a yellow solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 9.16 (1H, m), 8.59 (1H, d, J = 8.6 Hz), 7.86 (1H, dd, J = 8.5, 4.1 Hz), 7.37 (1H, m), 7.27 (4H, m), 4.66 (2H, d, J = 5.6 Hz), 3.85 (2H, m), 3.80 (2H, m), 3.62 (1H, m), 3.46 (1H, m), 2.27 (3H, m), and 1.67 (1H, m) ppm.

Step 3: N-{2-[2-(Dimethylamino)-2-oxoethyl]benzyl}-5- (1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide

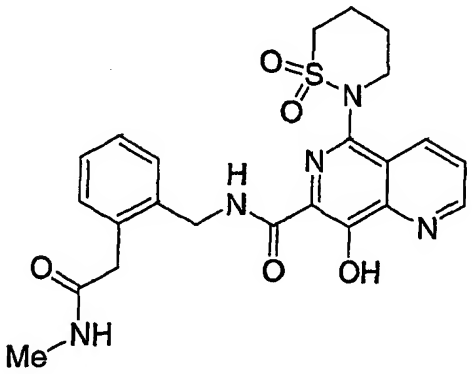
Dimethylamine gas was bubbled through a solution of {2-[({[5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy- 1,6-naphthyridin-7-yl]carbonyl}amino)-methyl]phenyl}acetic acid (27 mg, 0.07 mmol) and triethylamine (17 μL, 0.11 mmol) in dry DMF (0.5 mL) until the solution was saturated and (benzotiazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (33 mg, 0.07 mmol, BOP reagent) was added. The reaction was stirred for 30 minutes at room temperature after which a couple drops of water were added to quench the reaction. The solution was filtered through a glass fiber filter and the filtrate was purified by preparative HPLC (Gilson semi preparative HPLC system using a Waters Nova pak column (10x40 mm I.D. cartridges, C18, 6 μM pore size) eluting with 95-5% water (0.025% TFA) / acetonitrile (0.025% TFA) at 35 mL/min) to give the product as a yellow solid after freeze drying.

^{1}H NMR (DMSO-d6, 400 MHz) δ 9.18 (1H, m), 9.08 (1H, m), 8.61 (1H, m), 7.88 (1H, dd, J = 8.4, 4.2 Hz), 7.38 (1H, m), 7.24 (2H, m), 7.18 (1H, m), 4.60 (2H, m), 3.91 (2H, s), 3.61-3.55 (4H, m), 3.11 (3H, s), 2.83 (3H, s), 2.23 (3H, m), and 1.69 (1H, m) ppm.

APCI HRMS: calc'd for $C_{24}H_{27}N_5O_5S$ + H 498.1811, observed 498.1806.

EXAMPLE 6

5-(1,1-Dioxido-1,2-thiazinan-2-yl)-8-hydroxy- N-{2-[2-(methylamino)-2-oxoethyl]benzyl}-1,6-naphthyridine-7-carboxamide



In a manner similar to that described for Example 5 the title compound was prepared as a yellow solid.

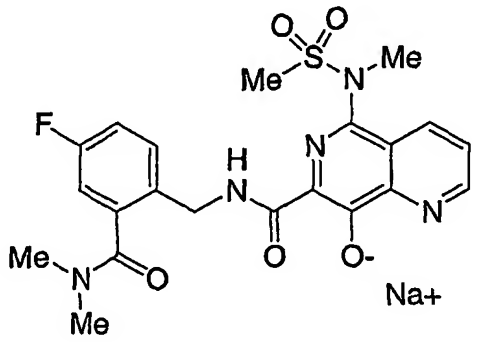
^{1}H NMR (DMSO-d6, 400 MHz) δ 9.35 (1H, m), 9.18 (1H, dd, J = 4.2, 1.7 Hz), 8.61 (1H, dd, J = 8.4, 1.7 Hz), 8.18 (1H, m), 7.88 (1H, dd, J = 8.4, 4.2 Hz), 7.41 (1H,

m), 7.26-7.23 (3H, m), 4.71 (2H, m), 4.19 (2H, m), 3.88 (1H, m), 3.66 (2H, s), 3.50 (1H, m), 2.60 (3H, d, J = 3.7 Hz), 2.25 (3H, m), and 1.68 (1H, m) ppm.

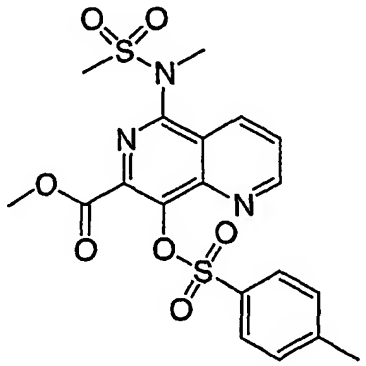
APCI HRMS: calc'd for $C_{23}H_{25}N_5O_5S$ + H 484.1663, observed 484.1649.

EXAMPLE 7

Sodium 7-[({2-[(dimethylamino)carbonyl]-4-fluorobenzyl}amino)carbonyl]- 5-[methyl(methylsulfonyl)amino]-1,6-naphthyridin-8-olate



Step 1: Methyl 5-[methyl(methylsulfonyl)amino]-8-{[(4-methylphenyl)sulfonyl]oxy}-1,6-naphthyridine-7-carboxylate

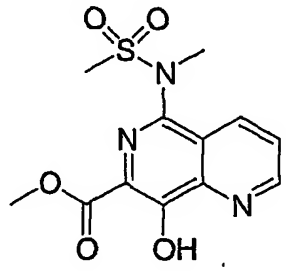


In a dried sealable pressure tube flushed with nitrogen was placed methyl 5-bromo-8-{[(4-methylphenyl)sulfonyl]oxy}-1,6-naphthyridine-7-carboxylate (500 mg, 1.14 mmol, prepared as described in Example 2, Step 2), N-methylmethanesulfonamide (168 mg, 1.54 mmol, prepared as in *J. Chem. Soc., Perkins Trans.* 1986, 2 (8): 1211-16), 2,2'-bipyridyl (241 mg, 1.54 mmol), dry DMF (3 mL) and copper(I) oxide (221 mg, 1.54 mmol). The tube was capped and heated to 85°C overnight. In the morning, the reaction was cooled and filtered through a glass

fiber filter, washing with chloroform. The filtrate was diluted with chloroform (about 100 mL total volume) and stirred with an EDTA solution (5 g EDTA in 100 mL water) for two hours or until the aqueous layer became aqua in color and the organic layer became yellow. The layers were separated and the aqueous layer was extracted twice more with chloroform. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (ISCO column, 110 g silica) eluting with a 0-5% MeOH / $CHCl_3$ gradient over 35 minutes. The concentrated fractions were triturated with methanol to give the product as a white solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 9.04 (1H, dd, J = 4.2, 1.5 Hz), 8.67 (1H, dd, J = 8.4, 1.5 Hz), 7.87 (1H, dd, J = 8.6, 4.2 Hz), 7.75 (2H, d, J = 8.2 Hz), 7.44 (2H, d, J = 8.6 Hz), 3.76 (3H, s), 3.36 (3H, s), 3.30 (3H, s) and 2.43 (3H, s) ppm.

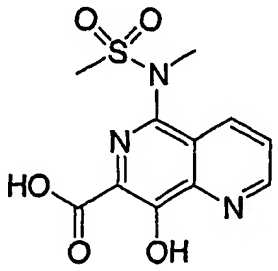
Step 2: Methyl 8-hydroxy-5-[methyl(methylsulfonyl)amino]-1,6-naphthyridine-7-carboxylate



A solution of sodium methoxide (122 mg, 2.26 mmol) in dry methanol (5 mL) was added to methyl 5-[methyl(methylsulfonyl)amino]-8-{[(4-methylphenyl)sulfonyl]oxy}-1,6-naphthyridine-7-carboxylate (420 mg, 0.90 mmol) dissolved in a minimum amount of DMF and the resulting solution was heated to 50°C for one hour. The reaction was cooled, glacial acetic acid (104 µL, 1.80 mmol) was added and the reaction was concentrated to dryness *in vacuo*. The resulting residue was triturated with ethanol and the solids were collected by vacuum filtration to give the desired product as a yellow solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 9.21 (1H, dt, J = 4.0, 1.6 Hz), 8.61 (1H, dt, J = 8.4, 1.6 Hz), 7.92 (1H, m), 3.94 (3H, d, J = 1.3 Hz), and 3.28 (6H, m) ppm.

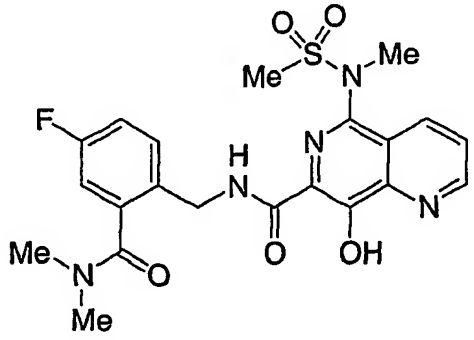
Step 3: 8-Hydroxy-5-[methyl(methylsulfonyl)amino]-1,6-naphthyridine-7-carboxylic acid



Sodium hydroxide (2.31mL, 2.31 mmol, 1N solution) was added to a suspension of methyl 8-hydroxy-5-[methyl(methylsulfonyl)amino]-1,6-naphthyridine-7-carboxylate (240 mg, 0.77 mmol) in a 1:1 solution of THF/methanol (5 mL) and the resulting mixture was heated overnight at 50°C. In the morning, the homogeneous solution was acidified to a pH = 4 using 1N HCl solution. The reaction was cooled and the solids that had precipitated out of solution were collected by vacuum filtration to give the desired product as an off-white solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 9.22 (1H, dd, J = 4.2, 1.5 Hz), 8.64 (1H, dd, J = 8.5, 1.4 Hz), 7.93 (1H, dd, J = 8.4, 4.2 Hz), 3.29 (3H, s), and 3.28 (3H, s) ppm.

Step 4: N-{2-[(Dimethylamino)carbonyl]-4-fluorobenzyl}-8- hydroxy-5-[methyl(methylsulfonyl)amino]-1,6-naphthyridine-7-carboxamide



In a manner similar to that described in Example 3, 8-hydroxy-5-[methyl(methylsulfonyl)amino]-1,6-naphthyridine-7-carboxylic acid was coupled with {2-[(dimethylamino)carbonyl]-4-fluorophenyl}methanaminium chloride (prepared as

described in Example 4) to give the desired product as an off-white solid which was taken on as is to the sodium salt.

LC/MS: calc'd for $C_{21}H_{22}FN_5O_5S$ 475.5, observed MH+ 476.3.

Step 5: Sodium 7-[({2-[(dimethylamino)carbonyl]-4-fluorobenzyl}amino)carbonyl]- 5-[methyl(methylsulfonyl)amino]-1,6-naphthyridin-8-olate

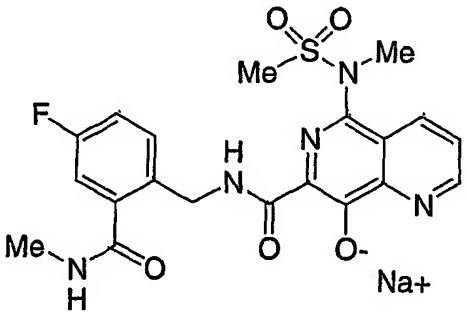
In a manner similar to that described for Example 3, the free base was converted to the desired salt, that was obtained as a yellow solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 12.00 (1H, bs), 8.79 (1H, m), 8.28 (1H, d, J = 8.1 Hz), 7.57 (1H, dd, J = 8.0, 3.8 Hz), 7.47 (1H, dd, J = 8.6, 5.7 Hz), 7.28 (1H, dt, J = 8.7, 2.8 Hz), 7.13 (1H, dd, J = 8.9, 2.7 Hz), 4.42 (2H, d, J = 5.0 Hz), 3.28 (3H, s), 3.16 (3H, s), 3.01 (3H, s), and 2.79 (3H, s) ppm.

ES HRMS: calc'd for C21H21FN5NaO5S 498.1218, observed 498.1218.

EXAMPLE 8

Sodium 7-[({4-fluoro-2-[(methylamino)carbonyl]benzyl}amino)carbonyl]- 5-[methyl(methylsulfonyl)amino]-1,6-naphthyridin-8-olate



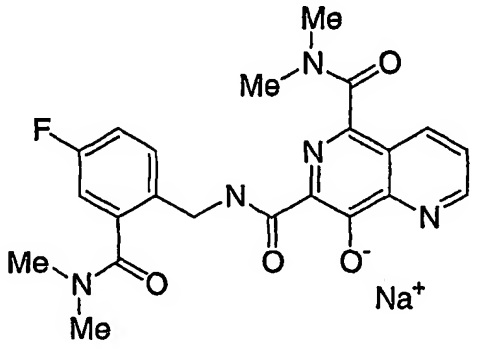
In a manner similar to that described for Example 7, the title compound was obtained as a yellow solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 8.79 (1H, dd, J = 4.2, 1.8 Hz), 8.29 (1H, dd, J = 8.3, 1.7 Hz), 7.57 (1H, dd, J = 8.4, 4.2 Hz), 7.40 (1H, dd, J = 8.6, 5.9 Hz), 7.20 (1H, dd, J = 9.7, 2.8 Hz), 7.14 (1H, dt, J = 8.6, 2.6 Hz), 4.63 (2H, m), 3.28 (3H, s), 3.16 (3H, s) and 2.78 (3H, s) ppm.

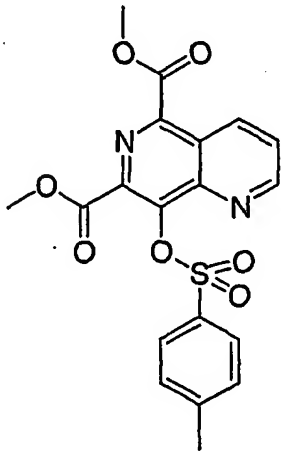
ES HRMS: calc'd for $C_{20}H_{20}FN_5O_5S$+H 461.1242, observed 462.1242.

EXAMPLE 9

Sodium 5-[(dimethylamino)carbonyl]-7-[({2-[(dimethylamino)carbonyl]-4-fluorobenzyl}amino)carbonyl]-1,6-naphthyridin-8-olate



Step 1: Dimethyl 8-{[(4-methylphenyl)sulfonyl]oxy}-1,6-naphthyridine-5,7-dicarboxylate



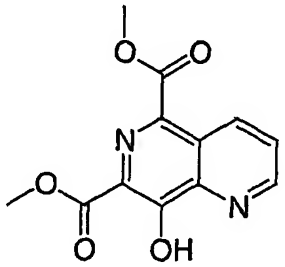
In an oven-dried high pressure bomb reactor apparatus was placed dry DMF and argon was bubbled through the solution. Methyl 5-bromo-8-{[(4-methylphenyl)sulfonyl]oxy}-1,6-naphthyridine-7-carboxylate (20g, 45.7 mmol, prepared as described in Example 2, Step 2), diisopropylethylamine (15.9 mL, 91.5 mmol), palladium acetate (0.256 g, 1.14 mmol), 1,1"-bis(diphenylphosphino)-ferrocene (dppf) (0.633g, 1.14 mmol) and methanol (9.3 mL, 228 mmol), in that

order, were added to the solution under a argon stream and the bomb was sealed. The bomb was purged two times with carbon monoxide to 200 psi, then charged with 200 psi carbon monoxide and heated to 80 degrees C (internal temperature) for 3 hrs in an oil bath. The vessel was cooled, the pressure was released and the crude reaction was concentrated to dryness. The residue was partitioned between water and EtOAc. The organic layer was washed with brine and dried over Na_2SO_4, then evaporated to give the crude product. The residue was dissolved in $CHCl_3$ and added to the top of a silica gel column (150mm x 4 inches) packed with $CHCl_3$. The column was eluted with 1:1 EtOAc/Hexanes. The fractions containing product were combined and evaporated. The tan/red residue was crystallized from hot ethyl acetate twice, then the solids were dissolved in EtOAc and treated with neutral decolorizing charcoal, filtered through a pad of celite and concentrated to give the product as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.26 (1H, dd, J = 1.7, 8.8 Hz), 9.04 (1H, dd, J = 1.7, 4.2 Hz), 7.82 (2H, d, J = 6.6 Hz), 7.67 (1H, dd, J = 4.0, 8.8 Hz), 7.31 (2H, d, J = 8.2 Hz), 4.09 (3H, s), 3.86(3H, s) and 2.46 (3H, s) ppm.

ES LRMS: M +H = 417.5

Step 2: Dimethyl 8-hydroxy-1,6-naphthyridine-5,7-dicarboxylate



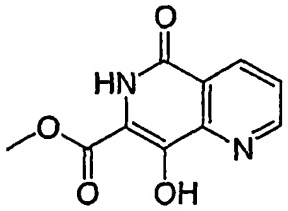
In an oven dried flask, a solution of dimethyl 8-{[(4-methylphenyl)sulfonyl]oxy}-1,6-naphthyridine-5,7-dicarboxylate (4.0g, 9.6 mmol) in trifluoroethanol (200 mL) was prepared. NaOMe/MeOH (5.24ml, 35% by weight solution in MeOH) was added with vigorous stirring at a rapid drip. The reaction was stirred at room temperature for 1 hr 10 min and then concentrated to dryness. The residue was immediately dissolved in 100 mL MeOH and the solution was scratched to initiate crystallization. The precipitated product was collected and washed with methanol, then dried under vacuum overnight. The yellow solid was suspended in water and treated with 2N HCl until the solids dissolved and the aqueous layer

remained acidic. The bright yellow solution was extracted with $CHCl_3$ until no more UV active material was removed. The organic layers were dried over Na_2SO_4, filtered and evaporated to give the product as an off-white solid.

^1H NMR (*d*-DMSO, 400MHz) δ 9.22 (1H, d, *J* = 4.0 Hz), 9.18 (dd, *J* = 1.1, 8.7 Hz), 7.95 (1H, dd, *J* = 8.8, 4.2 Hz), 3.96 (3H, s), 3.95 (3H, s) ppm.

Step 2': Alternative preparation of dimethyl 8-hydroxy-1,6-naphthyridine-5,7-dicarboxylate

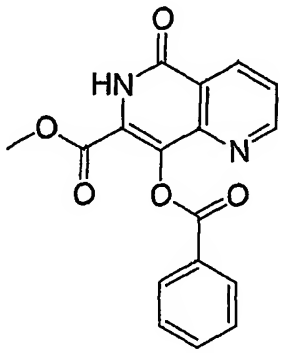
Step 2'-A: Preparation of methyl 8-hydroxy-5-oxo-5,6-dihydro-1,6-naphthyridine-7-carboxylate



This compound was prepared as described in M. Suzuki et.al., *Synthetic Communications*, 1978, pg. 461. To a solution of furo[3,4] pyridine-5,7-dione (130 g, 872 mmol) in anhydrous DMF (250 ml) was added 1 liter of dry THF and methyl isocyanoacetate (86.4 g, 872 mmol). This was stirred for 15 minutes at 40°C under nitrogen, followed by dropwise addition of DBU (132.8 g, 130.4 ml, 872 mmol) which was dissolved in THF (300 ml). After one hour the solvent was removed under reduced pressure and the resultant crude 2-[4-(methoxycarbonyl)-1,3-oxazol-5-yl]nicotinic acid and regioisomeric 3-[4-(methoxycarbonyl)-1,3-oxazol-5-yl]pyridine-2-carboxylic acid products were taken up into MeOH (1 liter). Concentrated HCl (12 M, 291 ml) was then added dropwise while the solution stirred at 55°C. This was stirred for 0.5 hours at which time the crude solids were collected by vacuum filtration. The desired regioisomer was purified by successive recrystallizations in methanol. This provided pure yellow solids.
TLC (silica, 90:10:3, dichloromethane, methanol, acetic acid), Rf (desired regioisomer) = 0.23, Rf (undesired regioisomer) = 0.62.

^{1}H NMR (DMSO, 400MHz) δ 10.66 (1H, bs), 9.11 (1H, dd, *J*=1.6, 4.5 Hz), 8.63 (1H, dd, *J*=1.6, 8.1 Hz), 7.80 (1H, dd, *J*=4.6 and 8.1 Hz), and 3.90 (3H, s) ppm.

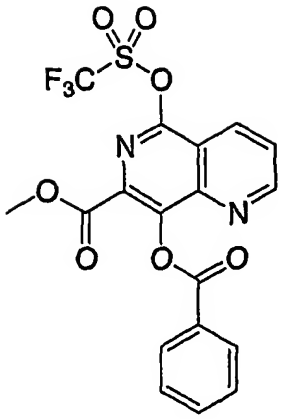
Step 2'-B: Preparation of methyl 8-(benzoyloxy)-5-oxo-5,6-dihydro-1,6-naphthyridine-7-carboxylate



To a mixture of the compound of Step 2'-A (20 g, 91 mmol) in dry DMF (250 ml) and dichloromethane (300 ml) under an atmosphere of argon at 0°C was added diisopropyl ethylamine (59 g, 82 ml, 455 mmol) dropwise followed by the addition of benzoic anhydride (21 g, 91 mmol) dissolved in dichloromethane (50 ml). The reaction was allowed to warm slowly to ambient temperature and stirred for 18 hours. The dichloromethane and 75% of the DMF was then removed in vacuo and white solids crystallized out of the deep red solution. The white solids were collected by vacuum filtration to give the title compound.

^{1}H NMR ($CDCl_3$, 400MHz) δ 9.36 (1H, bs), 8.99 (1H, dd, *J*=1.7, 4.5 Hz), 8.73 (1H, dd, *J*=1.7, 8.1 Hz), 8.28 (2H, d, *J*=8.4 Hz), 7.69 (1H, t, *J*=7.5 Hz), 7.59-7.54 (2H, m), 3.87 (3H, s) ppm.

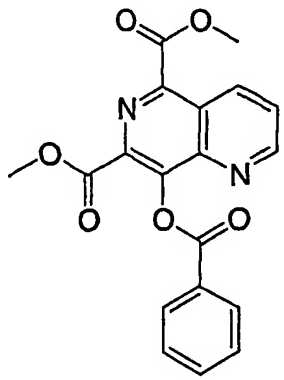
Step 2'-C: Preparation of methyl 8-hydroxy-5-{[(trifluoromethyl)sulfonyl]oxy}-1,6-naphthyridine-7-carboxylate



To a stirring suspension of the compound of Step 2'-B (25 g, 77 mmol) in dry dichoromethane (150 ml) under argon was added pyridine (31 ml, 385 mmol). The suspension was then cooled to 0°C and Tf_2O (32.6 g, 19.4 ml, 116 mmol) was added dropwise which caused the formation of a red color. The ice bath was then removed and after 1 hour the red solution was poured into a saturated aqueous solution of $NaHCO_3$ (200 ml). The organic phase was separated and the aqueous phase was extracted three times with chloroform. The combined organics were dried over sodium sulfate, filtered and concentrated to give a green solid.

^1H NMR ($CDCl_3$, 400MHz) δ 9.24 (1H, dd, *J*=1.6, 4.3 Hz), 8.53(1H, dd, *J*=1.6 8.5 Hz), 8.32 (2H, d, *J*=7.2 Hz), 7.81 (1H, dd, *J*=4.3 and 8.5 Hz), 7.70 (1H, m), 7.57 (m, 2H), and 3.92 (3H, s) ppm.

Step 2'-D: Preparation of dimethyl 8-(benzoyloxy)-1,6-naphthyridine-5,7-dicarboxylate



To a solution of the compound of Step 2'-D (11.9 g, 26 mmol) in DMF (50 ml) was added methanol (11 ml, 290 mmol), diisopropylethylamine (6.7 g, 9.3 ml, 52 mmol), $Pd(OAc)_2$ (0.58 g, 2.6 mmol), and 1,1'-bis(diphenylphosphino)-ferrocene (1.44 g, 2.6 mmol) while bubbling argon through the mixture. This was then placed in a bomb reactor and purged three times with carbon monoxide and finally filled to 80 p.s.i. and heated to 70°C for two hours. The reaction mixture was then poured into water (~150 ml). Ethyl acetate (50 ml) was then added to the mixture and the aqueous phase was extracted six times. The combined organics were dried over sodium sulfate, filtered and concentrated. The crude material was allowed to dry on the hi-vac overnight and was then suspended in ethyl acetate. The undesired solids (methyl 8-(benzoyloxy)-5-oxo-5,6-dihydro-1,6-naphthyridine-7-carboxylate) that did not dissolve were collected by vacuum filtration and set aside. This was repeated twice. To the EtOAc solution was then added hexanes and a few drops of diethyl ether and the mixture was placed in a sonicator for 15 minutes which allowed solids to crystallize out of the solution. The solids were collected by vacuum filtration.

^{1}H NMR ($CDCl_3$, 400MHz) δ 9.37 (1H, dd, *J*=1.5 and 8.8 Hz), 9.18(1H,d, *J*=4.2), 8.33 (1H, d, *J*=7.5 Hz), 7.74(1H, dd, *J*=4.2, and obscured Hz), 7.69 (2H, m), 7.56 (2H, m,), 4.12 (3H, s), 3.95 (3H,s).

Step 2'-E: Preparation of dimethyl 8-hydroxy-1,6-naphthyridine-5,7-dicarboxylate

Dimethyl 8-(benzoyloxy)-1,6-naphthyridine-5,7-dicarboxylate (2.0 g, 5.46 mmol) was dissolved in dry methanol (4.0 mL) in a pressure tube. Benzylamine (0.58 g, 5.46 mmol) was added and the reaction capped and heated to 80 degrees C under nitrogen for 16 hours. LCMS analysis indicated that the reaction was complete. The reaction was transferred to an Erlenmeyer flask and then diethyl ether was added to precipitate the product. Filtered and dried the solid *in vacuo* to obtain the desired compound.

^{1}H NMR (*d*-DMSO, 400MHz) δ 9.21 (1H, dd, *J* = 8.8, 1.46 Hz), 8.92 (1H, m), 7.71 (1H, dd, *J* = 8.8, 4.0 Hz), 3.86 (3H, s), 3.81 (3H, s) ppm.

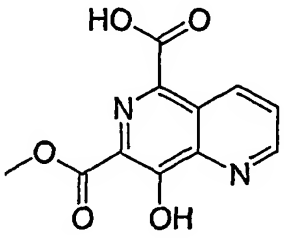
FAB HRMS exact mass calculated for C12H10N2O5 263.0663 (MH+), found 263.0663.

The compound prepared in Step 2 was spiked with the same compound prepared as in Step 2' and gave an NMR spectrum in DMSO identical to that described in Step 2. The compound prepared in Step 2 was spiked with the same compound prepared as in Step 2' and gave an NMR spectrum in CDCl3 shown below:

^{1}H NMR ($CDCl_3$, 400MHz) δ 9.45 (1H, dd, J = 8.8, 1.6 Hz), 9.24 (1H, dd, J = 4.2, 1.6 Hz), 7.78 (1H, dd, J = 8.8, 4.2 Hz), 4.15 (3H, s), 4.08 (3H, s) ppm.

ES HRMS: calc'd for $C_{12}H_{10}N_2O_5$: 263.0662, observed 263.0656.

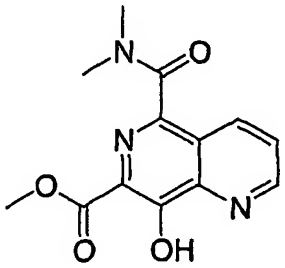
Step 3: 8-hydroxy-7-(methoxycarbonyl)-1,6-naphthyridine-5-carboxylic acid



To a suspension of dimethyl 8-hydroxy-1,6-naphthyridine-5,7-dicarboxylate (0.702 g, 2.7 mmol, prepared as described in Step 2 or in Step 2' above)) in a 1:1 solution of MeOH, THF (20 ml) was added 1N NaOH (8.03 mmol, 8.03 mL). The reaction was heated to 50 degrees C and stirred overnight. The suspension was concentrated and water (10 mL) was added to the residue. The reaction mixture was acidified to pH 3 with 1 N HCl and the resulting solids that precipitated from the solution were collected by vacuum filtration.

^{1}H NMR (DMSO-d6, 400 MHz) δ 9.23 (2H, m), 7.55 (1H, m), 3.96 (3H, s) ppm.

Step 4: Methyl 5-[(dimethylamino)carbonyl]-8-hydroxy-1,6-naphthyridine-7-carboxylate



To a solution of 8-hydroxy-7-(methoxycarbonyl)-1,6-naphthyridine-5-carboxylic acid (0.145 g, 0.584 mmol) in anhydrous DMF (2 mL) was bubbled in dry dimethylamine gas for 3 minutes. (1H-1,2,3-benzotriazol-1-yloxy)[tris-(dimethylamino)]phosphonium hexafluorophosphate (0.324 g, 0.759 mmol, BOP reagent) was then added and the solution was stirred for 30 minutes at room temperature. The yellow solids that had precipitated from the solution were dissolved with a few drops of water. The material was dissolved in a minimum amount of water/MeOH and filtered and purified by preparative HPLC (Gilson semi preparative HPLC system using a Waters Nova pak column (10x40 mm I.D.) cartridge, C18, 6 μM pore size) eluting with 95-5% water (0.025% TFA) / acetonitrile (0.025% TFA) at 30 mL/min). The fractions which contained product were then concentrated to give a brown sticky solid.

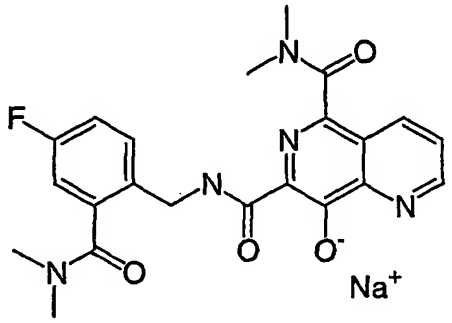
^{1}H NMR (DMSO-d6, 400 MHz) δ 9.23 (1H, m), 8.40 (1H, m), 7.88 (1H, m), 3.95 (3H, s), 3.13 (3H, s) and 2.83 (3H, s) ppm.

Step 5: 5-[(Dimethylamino)carbonyl]-8-hydroxy-1,6-naphthyridine-7-carboxylic acid

To a solution of methyl 5-[(dimethylamino)carbonyl]-8-hydroxy-1,6-naphthyridine-7-carboxylate (0.161 g, 0.585 mmol) in a 1:1 mixture of THF/MeOH (6 mL) was added 1 N NaOH (1.17 mmol, 1.2 mL). After stirring at 50^{0}C overnight the reaction was acidified with 1 N HCl to a pH of 3 and then concentrated to dryness. The material was then dissolved in a minimum amount of water/MeOH and then filtered and purified by preparative HPLC (Gilson semi preparative HPLC system using a Waters Nova pak column (10x40 mm I.D.) cartridge, C18, 6 μM pore size) eluting with 95-5% water (0.025% TFA) / acetonitrile (0.025% TFA) at 30 mL/min) to give the desired product. The pure product factions were then concentrated to give the desired product as a yellow solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 9.21 (1H, dd, J = 4.3, 1.6 Hz), 8.42 (1H, dd, J = 8.5, 1.6 Hz), 7.88 (1H, dd, J = 8.4, 4.2 Hz), 3.13 (3H, s), and 2.84 (3H, s) ppm.

Step 6: Sodium 5-[(dimethylamino)carbonyl]-7-[({2-[(dimethylamino)carbonyl]-4-fluorobenzyl}amino)carbonyl]-1,6-naphthyridin-8-olate



To a solution of 5-[(dimethylamino)carbonyl]-8-hydroxy-1,6-naphthyridine-7-carboxylic acid (0.049 g, 0.188 mmol) under nitrogen in anhydrous DMF (1.5 mL) was added {2-[(dimethylamino)carbonyl]-4-fluorophenyl}-methanaminium chloride (0.065 g, 0.281 mmol, prepared as described in Example 4), triethylamine (0.039 mL, 0.281 mmol), EDC (0.054 g, 0.281 mmol), and HOAT (0.038 g, 0.281 mmol). After two hours the reaction was purified by preparative HPLC (Gilson semi preparative HPLC system using a Waters Nova pak column (10x40 mm I.D.) cartridge, C18, 6 μM pore size) eluting with 95-5% water (0.025% TFA) / acetonitrile (0.025% TFA) at 30 mL/min) to give the desired product. The fractions which contained the product were concentrated to give a yellow solid. The solids were taken up in an aqueous saturated ammonium chloride solution and chloroform. After extracting a few additional times with chloroform, the combined organics were dried over sodium sulfate, filtered and concentrated to afford the free base. The free base was dissolved in acetonitrile and treated with a 1N NaOH solution (0.098 ml) which caused the solution to turn bright yellow. The solution was stirred for 15 minutes at room temperature and then the solvent was removed under reduced pressure to give the yellow sodium salt.

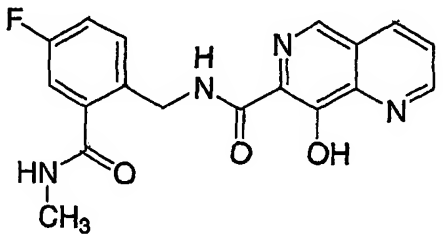
^{1}H NMR (DMSO-d6, 400 MHz) δ 12.10 (1H, m), 8.75 (1H, d J = 3.7 Hz), 8.19 (1H, d, J = 8.4 Hz), 7.47 (2H, m), 7.20 (1H, t, J = 7.7 Hz), 7.09 (1H, dd J = 9.2, 2.0

Hz), 4.42 (2H, d, J = 5.3 Hz), 3.31 (3H, s), 3.06 (3H, s), 3.00 (3H, s), and 2.78 (3H, s) ppm.

ES HRMS: calc'd for $C_{22}H_{21}FN_5O_4$ + Na: 462.1548, observed 462.1544.

EXAMPLE 10

N-{4-Fluoro-2-[(methylamino)carbonyl]benzyl}-8-hydroxy-1,6-naphthyridine-7-carboxamide

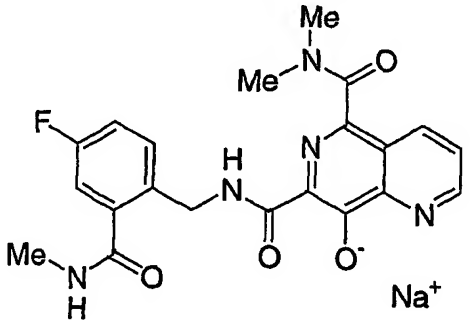


This compound was prepared by an amide formation coupling reaction with 8-hydroxy-1,6-naphthyridine-7-carboxylic acid and {4-fluoro-2-[(methylamino)carbonyl]phenyl}methanaminium chloride (prepared as described in Example 3) as previously described for the synthesis of Example 3.

^{1}H NMR (DMSO-d6, 400 MHz) δ 9.19 (2H, m), 8.70 (1H, s), 8.31 (1H, dd, J = 8.3, 1.5 Hz), 7.67 (1H, dd, J = 8.3, 4.3), 7.57 (1H, dd, J = 8.4, 5.5 Hz), 7.16 (1H, m), 6.42 (1H, bs), 4.71 (2H, d, J = 6.5 Hz), and 3.07 (3H, d J = 4.9 Hz) ppm.

EXAMPLE 11

Sodium 5-[(dimethylamino)carbonyl]-7-[({4-fluoro-2-[(methylamino)carbonyl]-benzyl}amino)carbonyl]-1,6-naphthyridin-8-olate



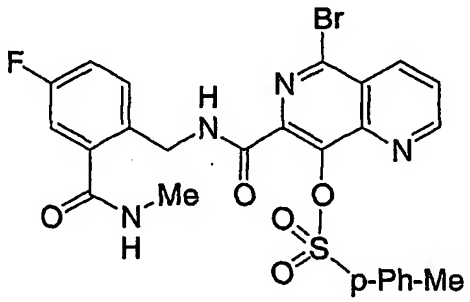
The title compound was prepared in a manner similar to the procedure set forth in Example 9.

^{1}H NMR (DMSO-d6, 400 MHz) δ 12.20 (1H, t, J = 5.9 Hz), 8.83 (1H, d, J = 4.2 Hz), 8.76 (1H, m), 8.19 (1H, m), 7.49-7.43 (2H, m), 7.26-7.18 (2H, m), 4.59 (2H, d, J = 5.9 Hz), 3.05 (3H, s), 2.90 (3H, s) and 2.81 (3H, d, J = 4.4 Hz) ppm.

ES HRMS: calc'd for $C_{21}H_{20}FN_5O_4$+H 426.1572, observed 426.1581.

The title compound was also prepared as the free acid as follows:

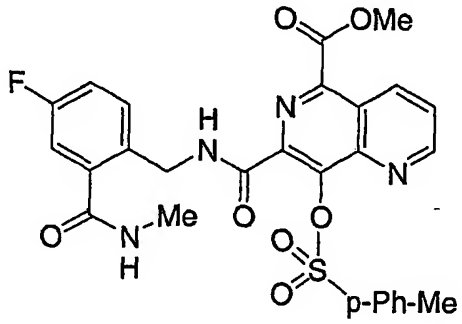
Step 1: 5-bromo-N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-8-{[(4-methylphenyl)sulfonyl]oxy}-1,6-naphthyridine-7-carboxamide



To a solution of 5-bromo-N-{4-fluoro-2-[(methylamino)carbonyl]-benzyl}-8-hydroxy-1,6-naphthyridine-7-carboxamide (0.93 g, 2.15 mmol) (see Step 2 of Example 20) and triethylamine (0.56 mL, 3.22 mmol) in methylene chloride (10 mL) was added p-tolune sulfonyl chloride (0.62 g, 3.22 mmol) slowly at 0 ^{0}C. The reaction mixture was stirred for 3 hrs. The mixture was partitioned between methylene chloride and 0.1 N HCl solution. The organic layer was washed with water and brine, dried and concentrated to give crude product. ISCO (gradient of 60% EtOAc/hexane to 100%) gave pure product.

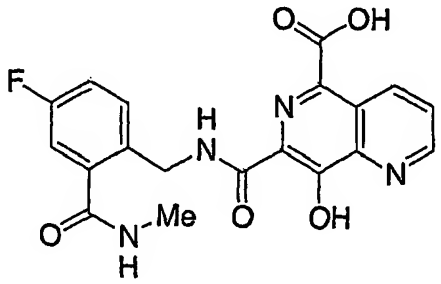
^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.03 (1H, dd, J= 1.5, 4.2 Hz), 8.53 (2H, m), 7.78 (2H, d, J= 8.3 Hz), 7.67 (1H, m), 7.50 (1H, m), 7.26 (2H, m), 7.14 (1H, dd, J= 2.7, 8.6 Hz), 7.07 (1H, dt, J= 2.8, 8.4 Hz), 6.90 (1H, d, J= 4.1 Hz), 4.60 (2H, d, J= 6.3 Hz), 3.00 (3H, d, J= 4.7 Hz), 2.46 (3H, s) ppm.

Step 2: Methyl 7-[({4-fluoro-2-[(methylamino)carbonyl]benzyl}-amino)carbonyl]-8-{[(4-methylphenyl)sulfonyl]oxy}-1,6-naphthyridine-5-carboxylate



To a solution of 5-bromo-N-{4-fluoro-2-[(methylamino)carbonyl] benzyl}-8-{[(4-methylphenyl)sulfonyl]oxy}-1,6-naphthyridine-7-carboxamide (0.10 g, 0.17 mmol), Pd(OAc)2 (4 mg, 0.017 mmol), DPPF (9 mg, 0.017 mmol), methanol (55 mg, 1.70 mmol) and diisopropylethylamine (44 mg, 0.34 mmol) in DMF (20 mL) in a steel bomb. The mixture was bubbled with N2 vigorously in a glass insert for the bomb, then charged with CO two times and released. After the third time, the bomb was kept at 120 psi. It was run overnight at 70 ^{0}C. The reaction mixture was concentrated and redissolved in methylene chloride. After filtration through a pad of celite washing with methylene chloride. The mixture was washed with water and brine, dried and concentrated to give crude product. ISCO (gradient of 60% EtOAc/hexane to 100%) gave pure product.
Mass ion (ES_+) of 567.2 for $M + H^+$.

Step 3: 7-[({4-fluoro-2-[(methylamino)carbonyl]benzyl}amino)carbonyl]-8-hydroxy-1,6-naphthyridine-5-carboxylic acid



To a solution of methyl 7-[({4-fluoro-2-[(methylamino)carbonyl] benzyl}amino)carbonyl]-8-{[(4-methylphenyl)sulfonyl]oxy}-1,6-naphthyridine-5-carboxylate) (100 mg, 0.177 mmol) in THF was added 1.0 M NaOH solution (3.53 mL, 3.53 mmol). The reaction mixture was stirred for 3 hrs. The mixture was partitioned between methylene chloride and water. The aqueous layer was acidified with 1.0 N HCl to pH1 and extracted with methylene chloride twice. The organic layer was washed with water and brine, dried and concentrated to give acid product. Mass ion (ES_+) of 399.1 for $M + H^+$.

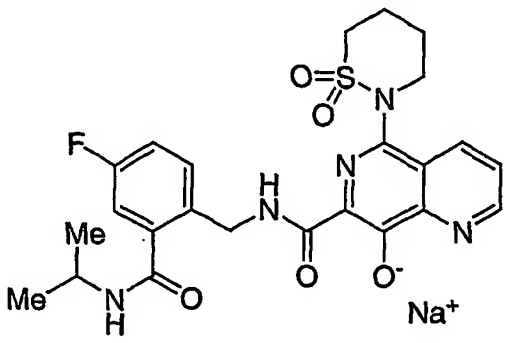
Step 4: N-7-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-8-hydroxy-N-5-,N-5-dimethyl-1,6-naphthyridine-5,7-dicarboxamide

A mixture of 7-[({4-fluoro-2-[(methylamino)carbonyl]benzyl}-amino)carbonyl]-8-hydroxy-1,6-naphthyridine-5-carboxylic acid (350 mg, 0.879 mmol), BOP (699 mg, 1.58 mmol) and diethylamine (0.66 mL, 1.318 mmol) was stirred at room temperature for 30 minutes. The mixture was partitioned between methylene chloride and 1.0 N HCl solution. The organic layer was washed with water and brine, dried and concentrated to give crude product. Purification by reverse phase chromatography eluting with (95:5 water/ CH_3CN to 5:95 water/CH_3CN, 0.1% TFA) gave pure product.

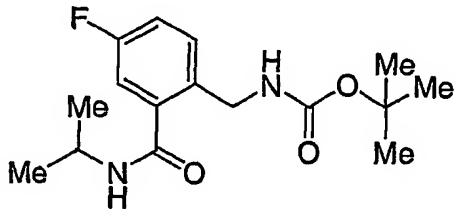
^1H NMR (DMSO-d6, 400 MHz) δ 13.80 (1H, s), 9.53 (1H, s), 9.18(1H, s), 8.53 (1H, m), 8.38(1H, d, *J*= 8.4 Hz), 7.83 (1H, m), 7.47-7.28 (3H, m), 4.65 (2H, d, *J*= 6.1 Hz), 3.13 (3H, s), 2.88 (3H, s), 2.80 (3H, d, *J*= 4.4 Hz) ppm.

EXAMPLE 12

Sodium 5-(1,1-dioxido-1,2-thiazinan-2-yl)-7-[({4-fluoro-2-[(isopropylamino)-carbonyl]benzyl}amino)carbonyl]-1,6-naphthyridin-8-olate



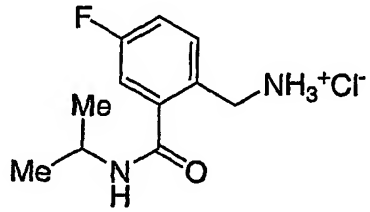
Step 1: *Tert*-butyl 4-fluoro-2-[(isopropylamino)carbonyl]benzylcarbamate



In an oven-dried high pressure bomb reactor apparatus was placed dry toluene (30 mL) and nitrogen was bubbled through the solution. Methyl 2-{[(tert-butoxycarbonyl)amino]methyl}-5-fluorobenzoate (4.0 g, 14.1 mmol, prepared as described in Example 3C, Step 4) and isopropylamine (12.0 mL, 0.14 mol) were added to the vessel. The bomb was sealed and heated to 70°C overnight. The vessel was cooled and the reaction was concentrated to dryness *in vacuo*. The residue was purifed by flash column chromatography (ISCO column, 120g silica) running a 0-30% acetone/hexane gradient over 30 minutes. The product fractions were concentrated to give the title compound as a white solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 8.32 (1H, d, J = 7.7 Hz), 7.23-7.34 (2H, m), 7.14-7.20 (2H, m), 4.19 (2H, d, J = 6.0), 4.02 (1H, m), 1.38 (9H, s), and 1.15 (6H, d, J = 6.6 Hz) ppm.

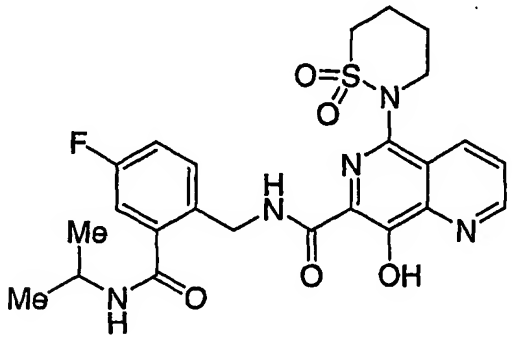
Step 2: {4-Fluoro-2-[(isopropylamino)carbonyl]phenyl}methanaminium chloride



This compound was prepared in a manner similar to that described in Example 3, Step 6 to afford a white solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 8.66 (1H, d, J = 7.5 Hz), 8.33 (3H, bs), 7.63 (1H, m), 7.40-7.45 (2H, m), 4.07 (1H, m), 4.01 (2H, s), and 1.17 (6H, d, J = 7.1 Hz) ppm.

Step 3: 5-(1,1-Dioxido-1,2-thiazinan-2-yl)-N-{4-fluoro-2-[(isopropylamino)carbonyl]benzyl}-8-hydroxy-1,6-naphthyridine-7-carboxamide



5-(1,1-Dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxylic acid (200 mg, 0.62 mmol, prepared as described in Example 3, Step 7), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (154 mg, 0.80 mmol), and 1-hydroxy-7-azabenzotriazole (109 mg, 0.80 mmol) were added to dry DMF (15 mL) and stirred for 30 minutes to preform the activated ester. {4-Fluoro-2-[(isopropylamino)carbonyl]phenyl}methanaminium chloride (168 mg, 0.68 mmol) and triethylamine (95μL, 0.68 mmol) were added and the reaction was stirred overnight at room temperature. The reaction was poured into water, the pH was adjusted to ~10 using 1N NaOH, and resulting solution was extracted several times with $CHCl_3$. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. The residue was redissolved in basic water and $CHCl_3$, acidified to pH = 4 using 1N HCl and extracted several times with $CHCl_3$. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to a whitish solid. Methanol was added to the flask and the flask was sonicated for 5 minutes. The resulting solids were collected by vacuum filtration to give the title compound as an off-white solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 13.71 (1H, s), 9.51 (1H, m), 9.19 (1H, m), 8.58 (2H, m), 7.89 (1H, m), 7.52 (1H, m), 7.35 (2H, m), 4.63 (2H, d, J = 5.5 Hz), 4.10 (1H, m), 3.92 (1H, m), 3.76 (1H, m), 3.66 (1H, m), 3.46 (1H, m), 2.33 (3H, m), 1.65 (1H, m), and 1.20 (6H, dd, J = 6.6, 1.7 Hz) ppm.

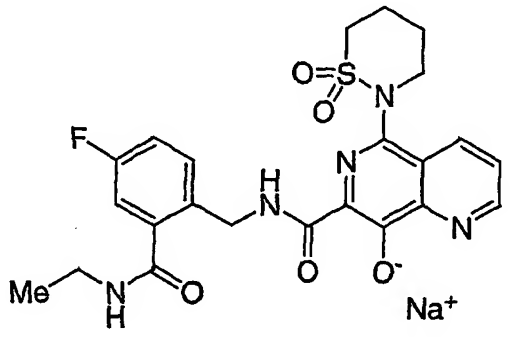
Step 4: Sodium 5-(1,1-dioxido-1,2-thiazinan-2-yl)-7-[({4-fluoro-2-[(isopropylamino)carbonyl]benzyl}amino)carbonyl]-1,6-naphthyridin-8-olate

5-(1,1-Dioxido-1,2-thiazinan-2-yl)-N-{4-fluoro-2-[(isopropylamino)carbonyl]benzyl}-8-hydroxy-1,6-naphthyridine-7-carboxamide (203 mg, 0.39 mmol) was suspended in acetone (2 mL) and sodium hydroxide (0.39 mL, 0.39 mmol, 1N aqueous solution) was added. The flask was gently warmed to make the solution homogeneous and the solution was then filtered through a glass fiber filter to remove any dust. The solution was stirred at room temperature until solids crashed out of solution. The solids were collected by vacuum filtration to give the title compound as a yellow solid.

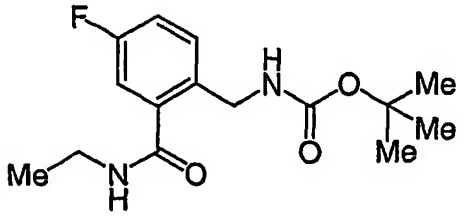
^{1}H NMR (DMSO-d6, 400 MHz) δ 12.16 (1H, bs), 8.78 (1H, dd, J = 4.2, 1.8 Hz), 8.68 (1H, m), 8.28 (1H, d, J = 8.2 Hz), 7.55 (1H, dd, J = 8.2, 4.2 Hz), 7.45 (1H, m), 7.23 (1H, dt, J = 8.6, 2.7 Hz), 7.17 (1H, m), 4.60 (2H, d, J = 5.7 Hz), 4.09 (1H, m), 3.85 (2H, m), 3.49 (1H, m), 3.22 (1H, m), 2.37 (1H, m), 2.22 (2H, m), 1.52 (1H, m) and 1.18 (6H, d, J = 6.6 Hz) ppm.

EXAMPLE 13

Sodium 5-(1,1-dioxido-1,2-thiazinan-2-yl)-7-[({2-[(ethylamino)carbonyl]-4-fluorobenzyl}amino)carbonyl]-1,6-naphthyridin-8-olate

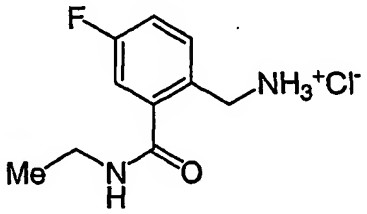


Step 1: *Tert*-butyl 2-[(ethylamino)carbonyl]-4-fluorobenzylcarbamate



This compound was prepared in a manner similar to that described in Example 12, Step 1 using ethylamine instead of isopropylamine. The reaction was concentrated to dryness and taken on without further purification.

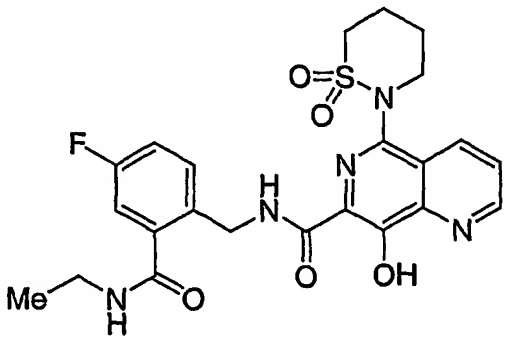
Step 2: {2-[(Ethylamino)carbonyl]-4-fluorophenyl}methanaminium chloride



This compound was prepared in a manner similar to that described in Example 3, Step 6 to afford an off-white solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 8.86 (1H, s), 8.38 (3H, bs), 7.64 (1H, m), 7.41-7.47 (2H, m), 4.03 (2H, d, J = 5.0 Hz), 3.29 (2H, m), and 1.15 (3H, t, J = 7.1 Hz) ppm.

Step 3: 5-(1,1-Dioxido-1,2-thiazinan-2-yl)-N-{2-[(ethylamino)carbonyl]-4-fluorobenzyl}-8-hydroxy-1,6-naphthyridine-7-carboxamide



In a similar manner as described for Example 12, Step 3 the title compound was prepared as a light yellow solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 13.71 (1H, s), 9.52 (1H, t, J = 6.4 Hz), 9.19 (1H, d, J = 4.2 Hz), 8.73 (1H, t, J = 5.2 Hz), 8.58, (1H, d, J = 8.6 Hz), 7.89 (1H, dd, J = 8.4, 4.2 Hz), 7.53 (1H, dd, J = 8.4, 5.6 Hz), 7.40 (1H, dd, J = 9.2, 2.4 Hz), 7.33 (1H, m), 4.64 (2H, d, J = 6.4 Hz), 3.94 (1H, m), 3.66-3.76 (2H, m), 3.46 (1H, m), 3.33 (2H, m), 2.33 (3H, m), 1.64 (1H, m), and 1.17 (3H, t, J = 7.2 Hz) ppm.

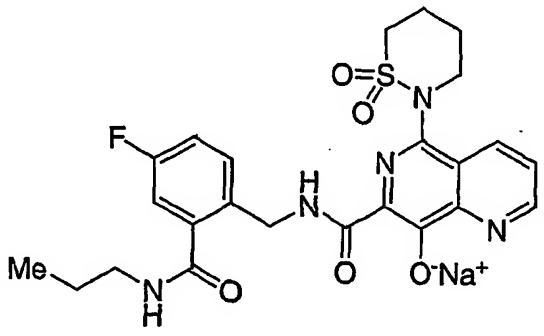
Step 4: Sodium 5-(1,1-dioxido-1,2-thiazinan-2-yl)-7-[({2-[(ethylamino)carbonyl]-4-fluorobenzyl}amino)carbonyl]-1,6-naphthyridin-8-olate

In a similar manner as described for Example 12, Step 4 the title compound was prepared as a light yellow solid.

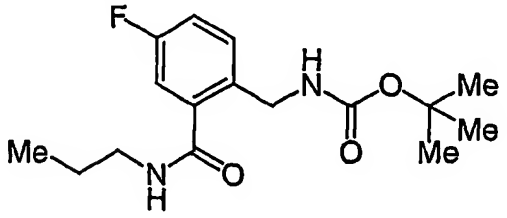
^{1}H NMR (DMSO-d6, 400 MHz) δ 12.11 (1H, s), 8.78 (1H, d, J = 4.0 Hz), 8.73 (1H, t, J = 5.0 Hz), 8.29 (1H, d, J = 8.2 Hz), 7.55, (1H, dd, J = 8.2, 4.1 Hz), 7.45 (1H, dd, J = 8.4, 5.9 Hz), 7.03-7.25 (2H, m), 4.61 (2H, d, J = 6.0 Hz), 3.78-3.86 (2H, m), 3.51 (1H, m), 3.29 (2H, m), 3.22 (1H, m), 2.45 (1H, m), 2.23 (2H, m), 1.52 (1H, m), and 1.15 (3H, t, J = 7.2 Hz) ppm.

EXAMPLE 14

Sodium 5-(1,1-dioxido-1,2-thiazinan-2-yl)-7-[({4-fluoro-2-[(propylamino)carbonyl]-benzyl}amino)carbonyl]-1,6-naphthyridin-8-olatem



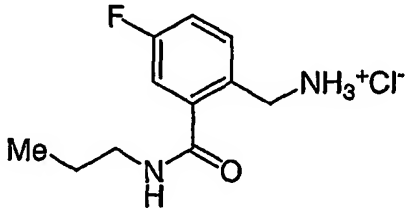
Step 1: *Tert*-butyl 4-fluoro-2-[(propylamino)carbonyl]benzylcarbamate



This compound was prepared in a manner similar to that described in Example 12, Step 1 using *n*-propylamine instead of isopropylamine, to afford the title compound as a white solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 8.45 (1H, s), 7.26-7.35 (2H, m), 7.17-7.25 (2H, m), 4.20 (2H, d, J = 6.1 Hz), 3.18 (2H, dd, J = 12.9, 6.7 Hz), 1.52 (2H, m), 1.39 (9H, s), and 0.90 (3H, t, J = 7.4 Hz) ppm.

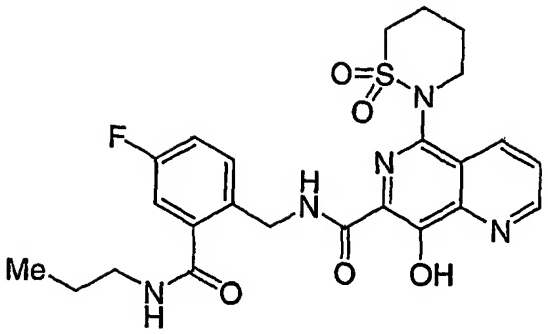
Step 2: {4-Fluoro-2-[(propylamino)carbonyl]phenyl}methanaminium chloride



This compound was prepared in a manner similar to that described in Example 3, Step 6 to afford an off-white solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 8.84 (1H, t, J = 5.2 Hz), 8.33 (3H, bs), 7.64 (1H, dd, J = 8.3, 5.6 Hz), 7.41-7.47 (2H, m), 4.02 (2H, t, J = 4.8 Hz), 3.23 (2H, dd, J = 12.9, 6.7 Hz), 1.56 (2H, m) and 0.92 (3H, t, J = 7.4 Hz) ppm.

Step 3: 5-(1,1-dioxido-1,2-thiazinan-2-yl)-N-{4-fluoro-2-[(propylamino)carbonyl]benzyl}-8-hydroxy-1,6-naphthyridine-7-carboxamide



In a similar manner as described for Example 12, Step 3 the title compound was prepared as a light yellow solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 13.70 (1H, bs), 9.52 (1H, t, J = 6.3 Hz), 9.19 (1H, d, J = 4.2 Hz), 8.74 (1H, t, J = 5.4 Hz), 8.58, (1H, d, J = 8.4 Hz), 7.89 (1H, dd, J = 8.6, 4.2 Hz), 7.53 (1H, m), 7.32-7.39 (2H, m), 4.63 (2H, d, J = 6.1 Hz), 3.92 (1H, m), 3.65-3.76 (2H, m), 3.46 (1H, m), 3.26 (2H, m), 2.33 (3H, m), 1.58 (3H, m), and 0.93 (3H, m) ppm.

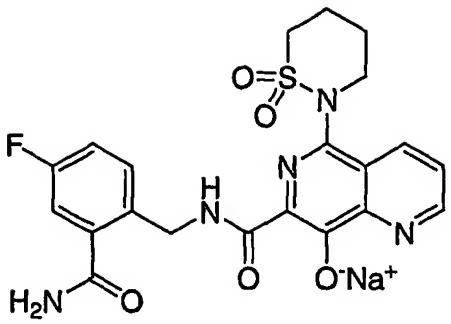
Step 4: Sodium 5-(1,1-dioxido-1,2-thiazinan-2-yl)-7-[({4-fluoro-2-[(propylamino)carbonyl]benzyl}amino)carbonyl]-1,6-naphthyridin-8-olate

In a similar manner as described for Example 12, Step 4 the title compound was prepared as a light yellow solid.

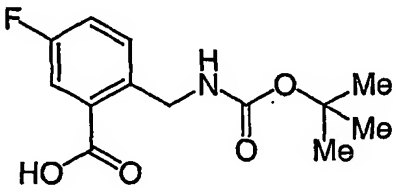
^{1}H NMR (DMSO-d6, 400 MHz) δ 12.18 (1H, bs), 8.78 (2H, m), 8.33 (1H, m), 7.60, (1H, m), 7.46 (1H, m), 7.23-7.27 (2H, m), 4.61 (2H, d, J = 5.7 Hz), 3.82-3.88 (2H, m), 3.55 (1H, m), 3.31 (1H, m), 3.25 (2H, m), 2.44 (1H, m), 2.24 (2H, m), 1.51-1.60 (3H, m), and 0.93 (3H, m) ppm.

EXAMPLE 15

Sodium 7-({[2-(aminocarbonyl)-4-fluorobenzyl]amino}carbonyl)-5-(1,1-dioxido-1,2-thiazinan-2-yl)-1,6-naphthyridin-8-olate



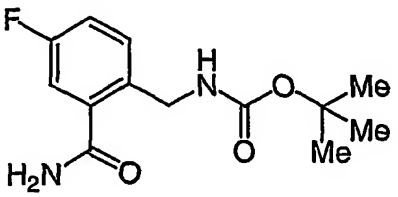
Step 1: 2-{[(*Tert*-butoxycarbonyl)amino]methyl}-5-fluorobenzoic acid



Methyl 2-{[(tert-butoxycarbonyl)amino]methyl}-5-fluorobenzoate (4.0 g, 14.1 mmol, prepared as described in Example 3C, Step 4) was dissolved in a 1:1 solution of methanol and THF (40 mL). Sodium hydroxide (15.5 mL, 15.5 mmol, 1N aqueous solution) was added and the reaction was stirred for 2 hours at room temperature. The reaction was acidified to a pH=4 using 3N HCl and concentrated to dryness *in vacuo*. The residue was purified by prep HPLC (Gilson semi preparative HPLC system using a Nova pak column (10x40 mm I.D. cartridge, C18, 6 μm pore size) eluting with 95-5% water (0.025% TFA) / acetonitrile (0.025% TFA) at 35 mL/min) in three runs. The fractions containing product were concentrated to afford the title compound as a white solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 13.32 (1H, bs), 7.59 (1H, dd, J = 9.5, 2.2 Hz), 7.41-7.44 (2H, m), 7.26 (1H, t, J = 6.1 Hz), 4.44 (2H, d, J = 6.1 Hz), and 1.40 (9H, s) ppm.

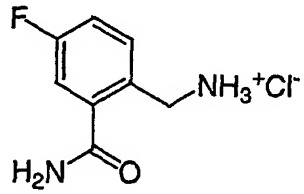
Step 2: *Tert*-butyl 2-(aminocarbonyl)-4-fluorobenzylcarbamate



2-{[(*Tert*-butoxycarbonyl)amino]methyl}-5-fluorobenzoic acid (800 mg, 2.97 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (854 mg, 4.46 mmol), and 1-hydroxy-7-azabenzotriazole (607 mg, 4.46 mmol) were added to dry DMF (10 mL) and stirred for 30 minutes to preform the activated ester. Ammonia gas was bubbled through the solution for 30 seconds and the reaction was allowed to stir for 5 minutes. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (ISCO column, 120g silica) running a gradient of 0-40% acetone/hexane over 35 min. The product fractions were concentrated to afford the title compound as a white solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 7.93 (1H, s), 7.56 (1H, s), 7.19-7.35 (4H, m), 4.25 (2H, d, J = 6. Hz), and 1.39 (9H, s) ppm.

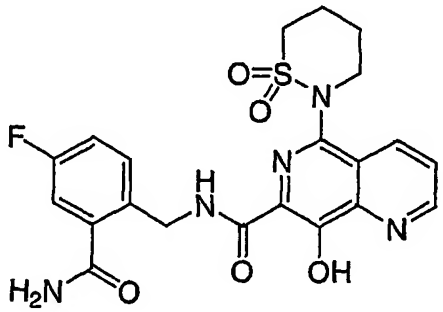
Step 3: [2-(Aminocarbonyl)-4-fluorophenyl]methanaminium chloride



This compound was prepared in a manner similar to that described in Example 3, Step 6 to afford a white solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 8.29 (4H, bs), 7.89 (1H, s), 7.63 (1H, dd, J = 8.4, 5.7 Hz), 7.52 (1H, dd, J = 9.4, 2.6 Hz), 7.44 (1H, dt, J = 8.5, 2.7 Hz), and 4.07 (2H, s) ppm.

Step 4: N-[2-(Aminocarbonyl)-4-fluorobenzyl]-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide



In a similar manner as described for Example 12, Step 3 the title compound was prepared as a light yellow solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 13.68 (1H, bs), 9.47 (1H, bs), 9.18 (1H, d, J = 4.2 Hz), 8.58 (1H, d, J = 8.4 Hz), 8.21, (1H, s), 7.88 (1H, dd, J = 8.4, 4.2 Hz), 7.77 (1H, s), 7.53 (1H, dd, J = 8.3, 5.7 Hz), 7.45 (1H, dd, J = 9.3, 2.2 Hz), 7.34 (1H, dt, J = 8.4, 2.1 Hz), 4.68 (2H, d, J = 6.2 Hz), 3.94 (1H, m), 3.77 (1H, m), 3.58 (1H, m), 3.45 (1H, m), 2.30-2.37 (3H, m), and 1.62 (1H, m) ppm.

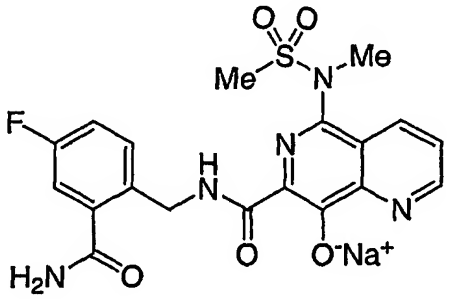
Step 5: Sodium 7-({[2-(aminocarbonyl)-4-fluorobenzyl]amino}carbonyl)-5-(1,1-dioxido-1,2-thiazinan-2-yl)-1,6-naphthyridin-8-olate

In a similar manner as described for Example 12, Step 4 the title compound was prepared as a light yellow solid.

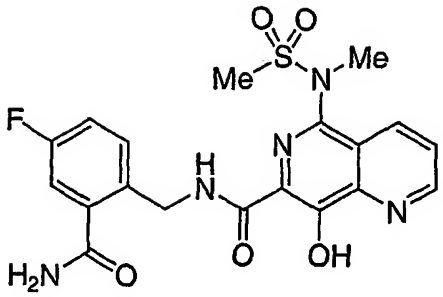
^{1}H NMR (DMSO-d6, 400 MHz) δ 12.12 (1H, bs), 8.78 (1H, d, J = 2.6 Hz), 8.30 (2H, m), 7.57, (2H, m), 7.46 (1H, dd, J = 9.2, 5.7 Hz), 7.22 (2H, m), 4.66 (2H, d, J = 5.5 Hz), 3.75-3.86 (2H, m), 3.54 (1H, m), 3.23 (1H, m), 2.43 (1H, m), 2.23 (2H, m), and 1.52 (1H, m) ppm.

EXAMPLE 16

Sodium 7-({[2-(aminocarbonyl)-4-fluorobenzyl]amino}carbonyl)-5-[methyl(methylsulfonyl)amino]-1,6-naphthyridin-8-olate



Step 1: N-[2-(Aminocarbonyl)-4-fluorobenzyl]-8-hydroxy-5-[methyl(methylsulfonyl)amino]-1,6-naphthyridine-7-carboxamide



In a similar manner as described for Example 12, Step 3, [2-(aminocarbonyl)-4-fluorophenyl]methanaminium chloride (from Example 15, Step 3) was coupled with 8-hydroxy-5-[methyl(methylsulfonyl)amino]-1,6-naphthyridine-7-carboxylic acid (from Example 7, Step 3) to afford the title compound.

^{1}H NMR (DMSO-d6, 400 MHz) δ 13.63 (1H, bs), 9.66 (1H, bs), 9.18 (1H, d, J = 2.8 Hz), 8.61 (1H, d, J = 8.4 Hz), 8.15 (1H, s), 7.88 (1H, dd, J = 8.5, 4.1 Hz), 7.75 (1H, s), 7.49 (1H, dd, J = 8.5, 5.5 Hz), 7.40 (1H, dd, J = 9.3, 2.8 Hz), 7.30 (1H, dt, J = 8.5, 2.6 Hz), 4.70 (2H, d, J = 6.4 Hz), 3.34 (3H, s), and 3.21 (3H, s) ppm.

Step 2: Sodium 7-({[2-(aminocarbonyl)-4-fluorobenzyl]amino}carbonyl)-5-[methyl(methylsulfonyl)amino]-1,6-naphthyridin-8-olate

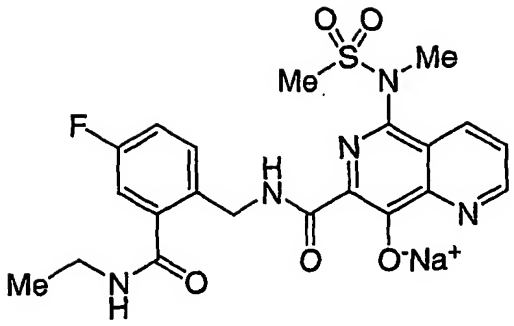
In a similar manner as described for Example 12, Step 4 the title compound was prepared as a light yellow solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 12.02 (1H, s), 8.79 (1H, d, J = 4.2 Hz), 8.30 (2H, m), 7.58, (2H, m), 7.45 (1H, m), 7.23 (2H, m), 4.65 (2H, d, J = 5.9 Hz), 3.27 (3H, s), and 3.16 (3H, s) ppm.

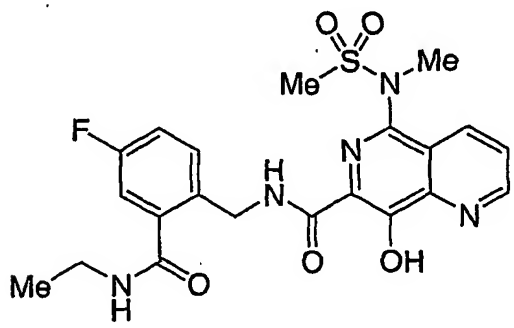
ES HRMS: calc'd for $C_{19}H_{18}FN_5O_5S$ + H: 448.1085, observed 448.1077

EXAMPLE 17

Sodium 7-({[2-(ethylaminocarbonyl)-4-fluorobenzyl]amino}carbonyl)-5-[methyl(methylsulfonyl)amino]-1,6-naphthyridin-8-olate



Step 1: N-{2-[(ethylamino)carbonyl]-4-fluorobenzyl}-8-hydroxy-5-[methyl(methylsulfonyl)amino]-1,6-naphthyridine-7-carboxamide



In a similar manner as described for Example 12, Step 3, {2-[(ethylamino)carbonyl]-4-fluorophenyl}methanaminium chloride (from Example 13, Step 2) was coupled with 8-hydroxy-5-[methyl(methylsulfonyl)amino]-1,6-naphthyridine-7-carboxylic acid (from Example 7, Step 3) to afford the title compound.

^{1}H NMR (DMSO-d6, 400 MHz) δ 9.67 (1H, s), 9.19 (1H, dd, J = 4.2, 1.6 Hz), 8.60-8.64 (2H, m), 7.89 (1H, m), 7.48 (1H, m), 7.27-7.35 (2H, m), 4.67 (2H, d, J = 6.0 Hz), 3.32-3.35 (5H, m), 3.23 (3H, s), 1.15 (3H, t, J = 7.2 Hz), and –1.13 (1H, s) ppm.

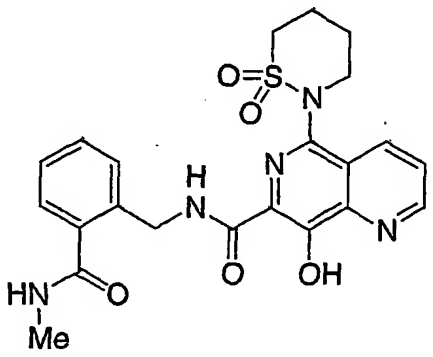
Step 2: Sodium 7-[({2-[(ethylamino)carbonyl]-4-fluorobenzyl}amino)carbonyl]-5-[methyl(methylsulfonyl)amino]-1,6-naphthyridin-8-olate

In a similar manner as described for Example 12, Step 4 the title compound was prepared as a light yellow solid.

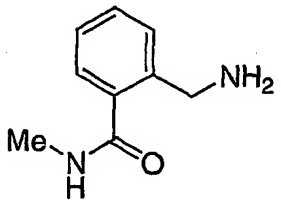
^{1}H NMR (DMSO-d6, 400 MHz) δ 12.08 (1H, bs), 8.76-8.80 (2H, m), 8.29 (1H, m), 7.58 (1H, m), 7.45 (1H, dd, J = 8.5, 5.8 Hz), 7.19-7.26 (2H, m), 4.61 (2H, d, J = 5.7 Hz), 3.28-3.34 (5H, m), 3.17 (3H, s), and 1.15 (3H, t, J = 7.2 Hz) ppm.

EXAMPLE 18

5-(1,1-Dioxido-1,2-thiazinan-2-yl)-8-hydroxy-*N*-{2-[(methylamino)carbonyl]benzyl}-1,6-naphthyridine-7-carboxamide



Step 1: 2-(Aminomethyl)-*N*-methylbenzamide



A suspension of 4-chloro-2-methylbenzoic acid (15.0 g, 87.9 mmol), *N*-bromosuccinimide (15.9 g, 89.3 mmol), and benzoyl peroxide (1.07 g, 4.4 mmol) in carbon tetrachloride (340 mL) was heated to reflux for 1 hour. Additional NBS (9.0 mmol) was added over this period to drive the reaction toward completion. The reaction was cooled, and filtered. The filtrate was washed once with aqueous sodium bicarbonate, followed by two washes with water. The organic fraction was dried over magnesium sulfate and then filtered. To this was added triethylamine (12.0 mL, 86.1 mmol), till the solution was basic and stirred overnight at room temperature. After which, water was added and extracted three times with chloroform. The combined organics were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The

product was recrystallized from a mixture of methanol, and diethyl ether as 5-chloro-2-benzofuran-1(3*H*)-one.

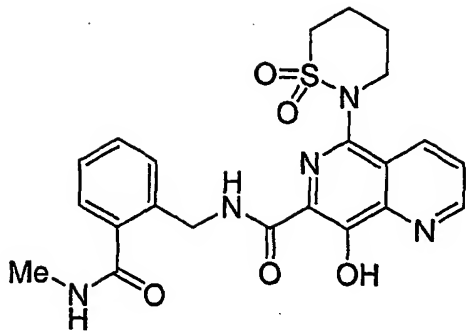
Methylamine gas was condensed into a sealed tube at –78 °C, and a solution of 5-chloro-2-benzofuran-1(3*H*)-one (6.68 g, 39.8 mmol) in methanol (30 mL) was added. The solution was slowly warmed to room temperature overnight. The reaction was concentrated *in vacuo*, and the residue was partitioned between water and and chloroform. After three extractions with chloroform, the combined organics were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford 4-chloro-2-(hydroxymethyl)-*N*-methylbenzamide.

To a solution of 4-chloro-2-(hydroxymethyl)-*N*-methylbenzamide (5.81 g, 29.2 mmol) in methylene chloride (200 mL) cooled in an ice bath, was added triethylamine (5.10 mL, 36.6 mmol) and methanesulfonyl chloride (2.50 mL, 32.3 mmol). After 90 min, the reaction was diluted with chloroform and partitioned with aqueous sodium bicarbonate and brine. After extracting three times with chloroform, the combined organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. To this residue was added DMF (50 mL) sodium azide (0.35 g, 5.4 mmol) and azidotrimethylsilane (2.6 mL, 19.6 mmol) portionwise with stirring at 40 °C for three days. The reaction was concentrated *in vacuo* and partitioned between chloroform and aqueous sodium bicarbonate. After extracting three times with chloroform, the combined organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography eluting with a 30-50% ethyl acetate/ hexane gradient. Fractions were concentrated *in vacuo* to afford 2-(azidomethyl)-4-chloro-*N*-methylbenzamide.

2-(Azidomethyl)-4-chloro-*N*-methylbenzamide (0.88 g, 3.94 mmol) was dissolved in ethanol (25 mL), degassed, treated with 10% Pd on carbon (80 mg), and put under one atmosphere of hydrogen. After one hour the reaction was filtered through Celite, and concentrated *in vacuo* to afford 2-(aminomethyl)-*N*-methylbenzamide as a white solid.

^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.74 (1H, br d, J = 4.2 Hz), 8.40 (2H, br s), 7.56 (4H, m), 4.05 (2H, s), and 2.80 (3H, d, J = 4.6 Hz).

Step 2: 5-(1,1-Dioxido-1,2-thiazinan-2-yl)-8-hydroxy-*N*-{2-[(methylamino)carbonyl]benzyl}-1,6-naphthyridine-7-carboxamide

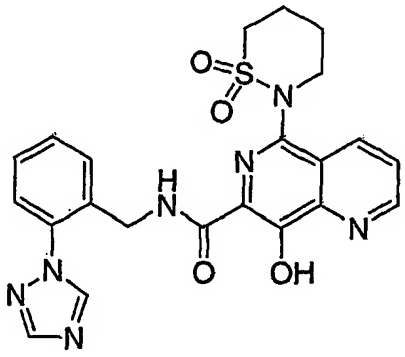


In a manner similar to that described in Example 3, 5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxylic acid was coupled with 2-(aminomethyl)-*N*-methylbenzamide to give the desired product as an off-white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 13.7 (1H, br s), 9.44 (1H, t, J = 6.5 Hz), 9.20 (1H, dd, J = 4.3, 1.6 Hz), 8.71 (1H, dd, J = 8.5, 1.6 Hz), 7.70 (1H, dd, J = 8.5, 4.3 Hz), 7.62 (1H, d, J = 7.3 Hz), 7.49 (2H, m), 7.37 (1H, dt, J = 7.5, 1.1 Hz), 6.13 (1H, br d, J = 4.2 Hz), 4.73 (1H, dd, J = 13.6, 7.2 Hz), 4.64 (1H, dd, J = 13.6, 6.2 Hz), 4.18 (1H, t, J = 13.0 Hz), 3.77 (1H, m), 3.63 (1H, d, J = 14.3 Hz), 3.23 (1H, d, J = 13.2 Hz), 3.03 (3H, d, J = 4.8 Hz), 2.70 (1H, m), 2.53 (2H, m), 1.70 (1H, d, J = 14.3 Hz).

ES HRMS: calc'd for $C_{22}H_{23}N_5O_5S$+H 470.1493, observed 470.1478.

EXAMPLE 19

5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-N-[2-(1H-1,2,4-triazol-1-yl)benzyl]-1,6-naphthyridine-7-carboxamide



A solution of 5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxylic acid (Example 3, Step 7) (0.05g, 0.155 mmol) and HOBT (0.063g, 0.464 mmol)in 2 mL DMF was cooled to 0°C and treated with EDC (0.039g,

0.2 mmol). The reaction was stirred for 2 hr and the amount of activated ester formed was monitored by LCMS. After 2 hours an additional 0.1 mmol of EDC was added, followed by 1-[2-(1H-1,2,4-triazol-1-yl)phenyl]methanamine (prepared as described in patent WO 02/064140 A1) (0.035g, 0.2 mmol). The reaction was stirred at 0°C for 3.5 hours, then filtered and purified by reverse phase chromatography (95:5 water/CH_3CN to 5:95 water/CH_3CN, 0.1% TFA) and lyophilized from dioxane to give the product as a white solid.

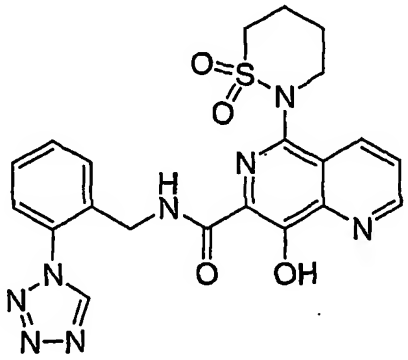
^1H NMR (DMSO-d6, 400 MHz) δ 13.6 (1H, bs), 9.19 (1H, dd, J = 1.7, 4.2 Hz), 9.14 (1H, t, J = 6.2 Hz), 9.05 (1H, s), 8.62 (1H, dd, J = 1.6, 8.6 Hz), 8.33 (1H, s), 7.88 (1H, dd, J = 4.2, 8.6 Hz) 7.6-7.5 (4H, m), 4.55 (2H, bt), 3.85 (2H, bs), 3.53 (2H, bs), 2.25 (2H, bs), 1.7 (1H, bs) ppm.

ES HRMS: calc'd for $C_{22}H_{21}N_7O_4S$ 480.1448, observed 480.1447..

CHN calc. For $C_{22}H_{21}N_7O_4S$ 0.2 dioxane 0.1 TFA C = 54.32, H = 4.50, N= 19.28; fnd. C = 54.25, H= 4.24, N = 19.32.

EXAMPLE 20

5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-N-[2-(1H-tetraazol-1-yl)benzyl]-1,6-naphthyridine-7-carboxamide



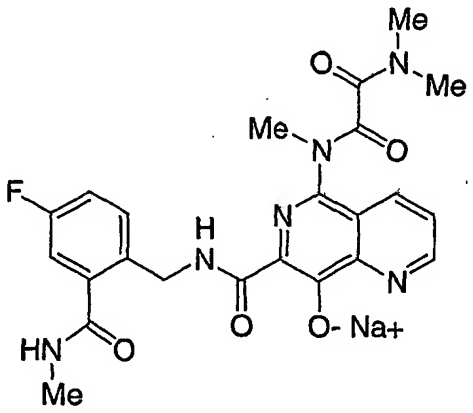
This compound was prepared as described for Example 19, using 1-[2-(1H-tetraazol-1-yl)phenyl]methanamine (prepared as described in WO 02/064140 A1) to give the title compound as a yellow solid.

^1H NMR (DMSO-d6, 400 MHz) δ 13.6 (1H, bs), 9.96 (1H, s), 9.19 (1H, dd, J = 1.7, 4.2 Hz), 9.05 (1H, t, J = 6.2 Hz), 8.61 (1H, dd, J = 1.7, 8.6 Hz), 7.89 (1H, dd, J = 4.2, 8.6 Hz), 7.72-7.53 (4H, m), 4.51 (2H, d, J =6.2 Hz), 3.85-3.6 (4H, bm), 3.5 (1H, bs), 2.3 (2H, bs), 1.7 (1H, bs) ppm.

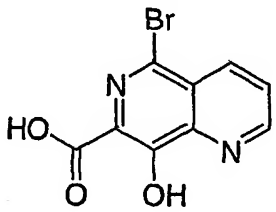
ES HRMS: calc'd for $C_{21}H_{20}N_8O_4S$ 481.1401, observed 481.1403.
CHN calc. For $C_{21}H_{20}N_8O_4S$ 0.1 dioxane 0.4 TFA C = 49.85, H = 3.99, N= 20.95; fnd. C = 49.80, H= 3.82, N = 20.89.

EXAMPLE 21

N1-{7-[({4-fluoro-2-[(methylamino)carbonyl]benzyl}amino)carbonyl]-8-hydroxy-1,6-naphthyridin-5-yl}-N1,N2,N2-trimethylethanediamide sodium salt

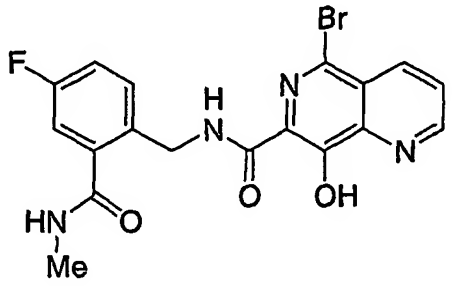


Step 1: 5-bromo-8-hydroxy-1,6-naphthyridine-7-carboxylic acid



A suspension of methyl 5-bromo-8-hydroxy-1,6-naphthyridine-7-carboxylic acid (Example 2, Step 1) (12.0g, 42.3 mmol) in THF (200ml) was treated with 127ml of 1N NaOH and 50 mL of MeOH and heated to 60° C overnight. 500mL of water was added and the thick suspension was heated at 60° C until all the solids dissolved. The solution was treated with portions of 6 N HCl until the pH of the solution stayed slightly acidic. Solids precipitated and were collected and air dried. ^{1}H NMR (DMSO-d6, 400 MHz) δ 13.5-12.5 (1H, broad), 9.23 (1H, d, J = 4.3 Hz), 8.57 (1H, d, J = 8.5 Hz), 7.99 (1H, dd, J = 4.3, 8.4 Hz)ppm.

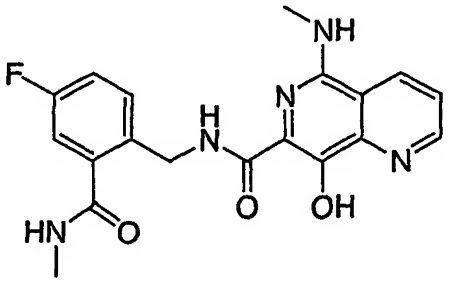
Step 2: 5-bromo-N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-8-hydroxy-1,6-naphthyridine-7-carboxamide



A suspension of 5-bromo-8-hydroxy-1,6-naphthyridine-7-carboxylic acid (1.1g, 4.1 mmol) in DMF (10mL) was cooled to 0°C and treated with HOBT (1.1g, 8.17 mmol) and EDC (0.76g, 4.9 mmol) with stirring for 40 minutes. Solid {4-fluoro-2-[(methylamino)carbonyl]phenyl}methanaminium chloride (Example 3, step 6) (1.1g, 4.9 mmol) and diisopropylethylamine (1.1mL, 6.1 mmol) were added and the reaction was allowed to warm to room temperature and stir for 3 days. The white solids that precipitated were collected, washed with DMF and dried under vacuum. The solid contained product and a small amount of the starting acid and was taken on to the next step.

^{1}H NMR (DMSO-d6, 400 MHz) δ 13.5 (1H, broad), 9.45 (1H, t, J = 6.0 Hz), 9.22 (1H, dd, J = 1.6, 4.2 Hz), 8.55 (2H, m), 7.95 (1H, dd, J = 4.3, 8.6 Hz), 7.49 (1H, dd, J = 5.7, 8.2 Hz), 7.3 (2H, m), 4.65 (2H, d, J = 6.3 Hz), 2.82 (3H, d, J = 4.6 Hz) ppm.
LRMS calc for $C_{18}H_{14}BrFN_4O_3$ = 432, observed m+1 = 433.

Step 3: N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-8-hydroxy-5-(methylamino)-1,6-naphthyridine-7-carboxamide

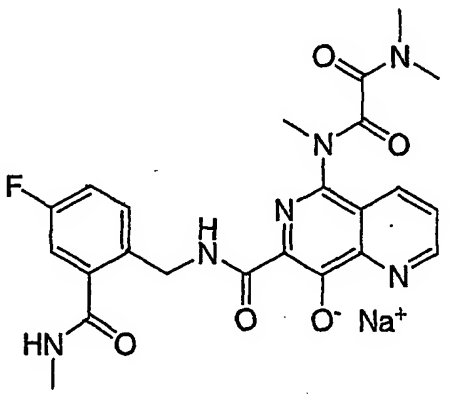


To a DMSO (2mL) solution of 5-bromo-N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-8-hydroxy-1,6-naphthyridine-7-carboxamide (0.5g, 1.15 mmol) in a 2-5mL microwave pressure vial was added methylamine (0.1g, 3.46 mmol, 3.3 M solution in MeOH), and the reaction was heated in a Smith Personal Chemistry microwave for 45 minutes at 200° C . The solution was purified by reverse phase chromatography (95:5 water/CH_3CN to 5:95 water/CH_3CN, 0.1% TFA). The fractions were concentrated, then dissolved in CH_3CN and MeOH and evaporated to dryness.

^1H NMR (DMSO-d6, 400 MHz) δ 12.3 (1H, broad), 9.33 (1H, t, J = 6.6 Hz), 9.03 (1H, dd, J = 1.5, 4.4 Hz), 8.65 (1H, dd, J = 1.5, 8.4 Hz), 8.56 (1H, m), 7.69 (1H, dd, J = 4.2, 8.4 Hz), 7.47 (1H, dd, J = 5.7, 8.4 Hz), 7.40 (1H, bs), 7.3 (2H, m), 4.61 (2H, d, J = 6.4 Hz), 2.99 (3H, s), 2.80 (3H, d, J = 4.4 Hz) ppm.

LRMS calc for $C_{19}H_{18}FN_5O_3$ = 483, observed m+1 = 484.

Step 4: N1-{7-[({4-fluoro-2-[(methylamino)carbonyl]benzyl}amino)-carbonyl]-8-hydroxy-1,6-naphthyridin-5-yl}-N1,N2,N2-trimethylethanediamide sodium salt



To a suspension of N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-8-hydroxy-5-(methylamino)-1,6-naphthyridine-7-carboxamide (0.21g, 0.548 mmol) in THF (40 mL) cooled to –78°C was added diidopropylethylamine (0.57 mL, 3.29 mmol). Methyl chloro(oxo)acetate (0.2 mL, 2.2 mmol) in 2 mL THF was added dropwise and the reaction was allowed to warm slowly to room temperature and stirred overnight, then cooled to zero and treated with the base and Methyl chloro(oxo)acetate again for 1 hr. The reaction was evaporated and the residue was taken onto the next step. The intermediate 7-[({4-fluoro-2-[(methylamino)carbonyl]-

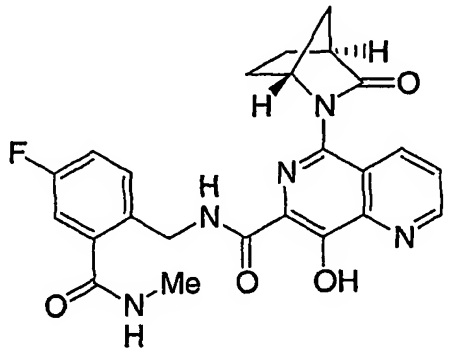
benzyl}amino)carbonyl]-5-[[methoxy(oxo)acetyl](methyl)amino]-1,6-naphthyridin-8-yl methyl oxalate could be detected by LCMS (MS calculated for C25H22FN5O9 = 555, observed m+1 = 556). The crude material was dissolved in MeOH (50 mL) in a heavy walled flask, cooled to 0°C and saturated with dimethylamine gas and the flask was sealed and the reaction warmed to room temperature for 1 hr. The solution was concentrated and the product purified by reverse phase chromatography (95:5 water/CH_3CN to 5:95 water/CH_3CN, 0.1% TFA). The fractions were concentrated and the residue was suspended in acetone and treated with 1.05 equivalents of aqueous NaOH, warmed to 50°C briefly and concentrated to give a yellow solid.

^1H NMR (DMSO-d6, 400 MHz) δ 12.1 (1H, broad), 8.79 (1H, m), 8.74 (1H, m), 8.06 (1H, d, J = 8.7 Hz), 7.54 (1H, dd, J = 3.7, 8.0 Hz), 7.40 (1H, app. t. J = 7.0 Hz) 7.21 (3H, m), 4.58 (2H, bs), 3.29 (3H, s), 3.32 (3H, s), 3.16 (3H, s), 2.80 (3H, d, J = 4.3 Hz) ppm.

ES HRMS: calc'd for $C_{23}H_{23}FN_6O_5$ 483.1782, observed 483.1780.

EXAMPLE 22

N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-8-hydroxy-5-[(1R,4S)-3-oxo-2-azabicyclo[2.2.1]hept-2-yl]-1,6-naphthyridine-7-carboxamide



A mixture of 5-bromo-N-{4-fluoro-2-(methylamino)carbonyl]-benzyl}-8-hydroxy-1,6-naphthyridine-7-carboxamide (0.12 g, 0.23 mmol) (Example 21, Step 2), copper oxide (0.12 g, 0.83 mmol) and (1R,4S)-3-oxo-2-azabicyclo[2.2.1]heptane (62 mg, 0.55 mmol) in pyridine (5mL) was degassed with vacuum/nitrogen cycle four times and heated to 100 ^{0}C and stirred for 23 hrs. The mixture was cooled to room temperature. Celite was added to the mixture. After filtration through a pad of celite with washing by methylene chloride, a brown color

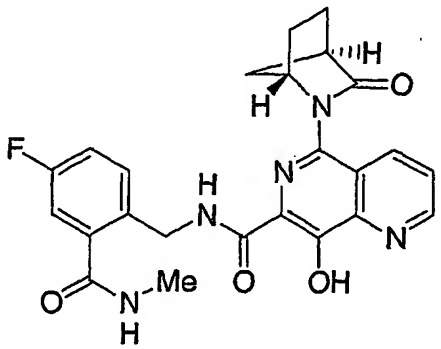
solution was obtained. Saturated EDTA solution was added and stirred for 30 minutes. The mixture was partitioned between methylene chloride and EDTA solution. The organic layer was washed with EDTA solution, water and brine, dried and concentrated to give crude product. Purification by reverse phase chromatography eluting with (95:5 water/ CH3CN to 5:95 water/CH3CN, 0.1% TFA) gave pure product.

^{1}H NMR (CD_3OD, 400 MHz) δ 9.07 (1H, s), 8.45 (1H, d, *J*= 8.8 Hz), 7.78 (1H, m), 7.57 (1H, m), 7.28 (1H, d, *J*= 9.1 Hz), 7.20 (1H, m), 4.65 (2H, d, *J*= 9.2 Hz), 2.95 (1H, s), 2.84 (3H, s), 2.55 (1H, m), 2.24 (2H, d, *J*= 8.4 Hz), 2.14 (2H, d, *J*= 9.4 Hz), 1.72 (2H, m) ppm.

HRMS: calc'd for $C_{24}H_{22}FN_5O_4$ + 1H = 464.1729, observed 464.1741.

EXAMPLE 23

N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-8-hydroxy-5-[(1S,4R)-3-oxo-2-azabicyclo[2.2.1]hept-2-yl]-1,6-naphthyridine-7-carboxamide



In a manner similar to that described in Example 2, the mixture 5-bromo-N-{4-fluoro-2-(methylamino)carbonyl]benzyl}-8-hydroxy-1,6-naphthyridine-7-carboxamide (100 mg, 0.231 mmol) (Example 21, Step 2), copper oxide (99 mg, 0.692 mmol), and(1S,4R)-3-oxo-2-azabicyclo[2.2.1]heptane (77 mg, 0.692 mmol) in pyridine (5 mL) was degassed with vacuum/nitrogen cycle for four times and heated to 100 ^{0}C and stirred for 23 hrs. The mixture was cooled to room temperature. Celite was added to the mixture. After filtration through a pad of celite with washing by methylene chloride, a brown color solution was obtained. Saturated EDTA solution was added and stirred for 30 minutes. The mixture was partitioned between methylene chloride and EDTA solution. The organic layer was washed with EDTA

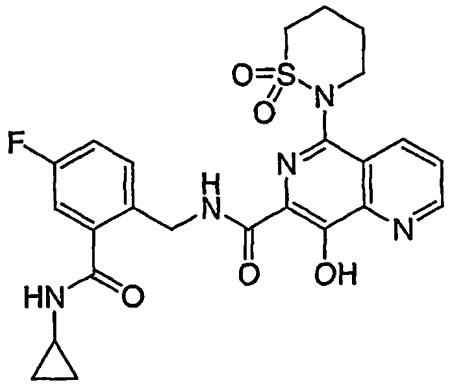
solution, water and brine, dried and concentrated to give crude product. Purification by reverse phase chromatography eluting with (95:5 water/ CH3CN to 5:95 water/CH3CN, 0.1% TFA) gave pure product.

^{1}H NMR (DMSO-d6, 400 MHz) δ 13.35 (1H, s), 9.36 (1H, t, *J*= 6.2 Hz), 9.13 (1H, d, *J*= 2.7 Hz), 8.60 (1H, d, *J*= 4.4 Hz), 8.33 (1H, d, *J*= 8.5 Hz), 7.50 (1H, dd, *J*= 2.8, 5.7 Hz), 7.37 (1H,dd, *J*= 2.6, 6.6 Hz), 7.33 (1H, d, *J*= 2.7 Hz), 7.29 (1H, dd, *J*= 2.7, 8.3 Hz), 4.64 (2H, d, *J*= 9.4 Hz), 3.80 (2H, s), 2.91 (1H, s), 2.81 (3H, s), 2.22 (1H, d, *J*= 9.4 Hz), 2.04 (2H, d, *J*= 8.4 Hz), 1.64 (2H, d, *J*= 9.4 Hz) ppm.

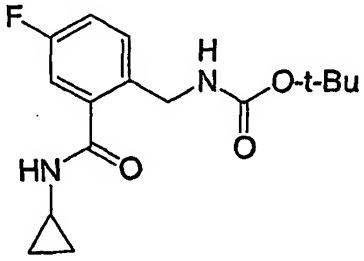
HRMS: calc'd for $C_{24}H_{22}FN_5O_4$ + 1H = 464.1729, observed 464.1711.

EXAMPLE 24

N-{2-(cyclopropylamino)carbonyl]-4-fluorobenzyl}-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide



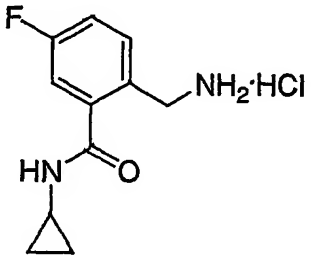
Step 1: t-Butyl 2-[(cyclopropylamino)carbonyl]-4-fluorobenzylcarbamate



To a solution of bis-tert-butyl 2-[methoxycarbonyl]-4-fluorobenzyl-carbamate (2.00 g, 5.22 mmol) (Example 3A, Step 2) in MeOH in a pressure glass flask was added cyclopropylamine (3.54 mL, 52.16 mmol). After stirring overnight, the reaction was not complete. 5.0 eq. of amine was added and stirred for two days.

The mixture was partitioned between methylene chloride and water. The organic layer was washed with water and brine, dried and concentrated to give pure product.

Step 2: {2-[(cyclopropylamino)carbonyl]-4-fluorobenzyl}methanaminium chloride



To a solution of t-butyl 2-[(cyclopropylamino)carbonyl]-4-fluorobenzylcarbamate (2.00 g, 5.22 mmol) in EtOAc was bubbled with HCl gas until the solution was saturated at 0 ^{0}C. The solution was concentrated to give a solid product. ^{1}H NMR (DMSO-d6, 400 MHz) δ 8.86 (1H, d, *J*= 3.8 Hz), 8.39 (3H, s), 7.63 (1H, m), 7.43 (2H, m), 4.02 (2H, d, *J*= 5.3 Hz), 2.87 (1H, m), 0.70 (2H, m), 0.62 (2H, m) ppm.

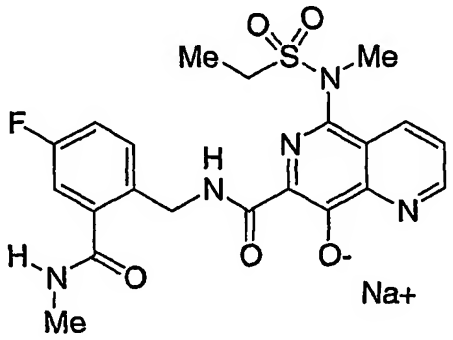
Step 3: N-{2-(cyclopropylamino)carbonyl]-4-fluorobenzyl}-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide

To a solution of 5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxylic acid (367 mg, 1.135 mmol) in DMF (10 mL) under N2 was added EDC (211 mg, 1.362 mmol), HOAT (463 mg, 3.405 mmol). After 20 minutes LC showed the reaction had gone to the activated ester mostly. Added another 0.5 eq. of EDC followed by the immediate addition of {2-[(cyclopropylamino)carbonyl]-4-fluorobenzyl}methanaminium chloride (333 mg, 1.362 mmol) and diisopropylethylamine (109 mg, 0.842 mmol). After a few minutes the reaction was done. The mixture was partitioned between chloroform and 1 N HCl solution. The organic layer was washed with water and brine, dried and concentrated to give crude product . Purification by reverse phase chromatography eluting with (95:5 water/ CH3CN to 5:95 water/CH3CN, 0.1% TFA) gave pure product.

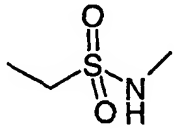
^{1}H NMR (DMSO-d6, 400 MHz) δ 9.19 (1H, s), 9.18(1H, t, *J*= 2.5 Hz), 8.73 (1H, d, *J*= 3.7 Hz), 8.58 (1H, d, *J*= 8.5 Hz), 7.88 (1H, dd, *J*= 4.2, 8.5 Hz), 7.52 (1H, m), 7.33 (2H, m), 4.63 (2H, d, *J*= 6.3 Hz), 4.02-3.52 (6H, m), 2.88 (2H, s), 1.63 (1H, m), 0.72-0.62 (4H, m) ppm.

EXAMPLE 25

Sodium 5-[(ethylsulfonyl)(methyl)amino]-7-[({4-fluoro-2-[(methylamino)carbonyl]-benzyl}amino)carbonyl]-1,6-naphthyridin-8-olate



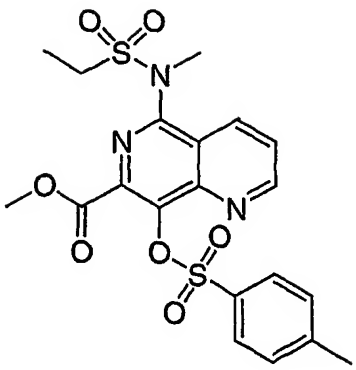
Step 1: N-methylethanesulfonamide



To ethanesulfonyl chloride (10 gm, 77.8 mmol) cooled to zero degrees was added dropwise a 14% weight solution of methylamine in water (100 mL). The reaction was stirred in a 90 degree oil bath for 1 hour and then cooled and extracted with methylene chloride. The organic was dried over magnesium sulfate and carefully evaporated under reduced pressure to give the desired product as a volatile oil.

^{1}H NMR (DMSO-d6, 400 MHz) δ 4.72 (1H, bs), 3.05 (2H, q, *J*= 7.5 Hz), 2.80 (3H, dd, *J*=5.3, 1.8 Hz), 1.37 (3H, t, *J*=7.3 Hz) ppm.

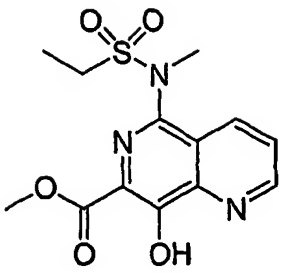
Step 2: Methyl 5-[(ethylsulfonyl)(methyl)amino]-8-{[(4-methylphenyl)sulfonyl]oxy}-1,6-naphthyridine-7-carboxylate



In a dried sealable pressure tube flushed with argon was placed methyl 5-bromo-8-{[(4-methylphenyl)sulfonyl]oxy}-1,6-naphthyridine-7-carboxylate (2.0g, 4.57mmol), prepared as described in Example 2, Step 2), N-methylethanesulfonamide (1.13 g, 9.15 mmol), dry DMF (4 mL) and copper(I) oxide (785 mg, 5.49 mmol) and 2,2'bipyridyl (857 mg, 5.49 mmol). The tube was capped and heated to 118°C for 2 hours. The reaction was cooled and filtered through a glass fiber filter, washing with chloroform. The filtrate was diluted with chloroform (about 100 mL total volume) and stirred with an EDTA solution (5 g EDTA in 100 mL water) for two hours or until the aqueous layer became aqua in color and the organic layer became yellow. The layers were separated and the aqueous layer was extracted twice more with chloroform. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was redissolved in 2 mL of DMSO and purified by preparative HPLC (Gilson semi preparative HPLC system using a Waters Nova pak column (10x40 mm I.D. cartridges, C18, 6 μM pore size) eluting with 95-5% water (0.025% TFA) / acetonitrile (0.025% TFA) at 35 mL/min) and the desired fractions were freeze dried to give the product as a yellow powder.

^{1}H NMR (DMSO-d6, 400 MHz) δ 9.03 (1H, dd, J = 4.4, 1.6 Hz), 8.65 (1H, dd, J = 8.6, 1.6 Hz), 7.86 (1H, dd, J = 8.4, 4.2 Hz), 7.75 (2H, d, J = 8.2 Hz), 7.44 (2H, d, J = 8.2 Hz), 3.76 (3H, s), 3.55 (2H, q, J= 7.5 Hz), 3.39 (3H, s), 2.43 (3H, s), and 1.3 (3H, t, J=7.33 Hz) ppm.

Step 3: Methyl 8-hydroxy-5-[methyl(ethylsulfonyl)amino]-1,6-naphthyridine-7-carboxylate



A solution of sodium methoxide (479 mg, 8.86 mmol) in dry methanol (18 mL) was added to methyl 5-[methyl(ethylsulfonyl)amino]-8-{[(4-methylphenyl)sulfonyl]oxy}-1,6-naphthyridine-7-carboxylate (1.7 g, 3.54 mmol) dissolved in a minimum amount of DMF and the resulting solution was heated to 50°C for 5 minutes. The reaction was cooled, glacial acetic acid (0.433 mL, 7 mmol) was added followed by water (0.936 mL) over 15 minutes at 25 degrees C . The resulting solid was collected by filtration and washed with 1:1 water methanol and dried in vacuo to give the desired product as a yellow solid.

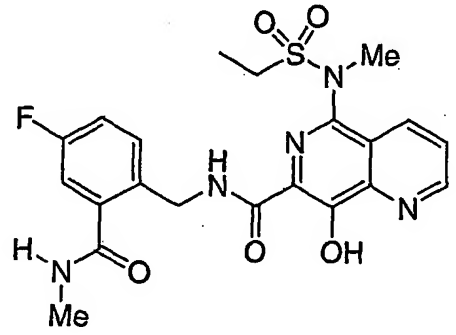
^{1}H NMR (DMSO-d6, 400 MHz) δ 11.55 (1H, bs), 9.22 (1H, dt, J = 4.1, 2.8 Hz), 8.60 (1H, d, J = 8.4 Hz), 7.94 (1H, dd, J= 8.4, 4.2 Hz), 3.94 (3H, d, J = 1.3 Hz), 3.50 (2H, q, J= 7.2 Hz), 3.29 (3H, bs), 1.31 (3H, t, J= 7.3 Hz) ppm.

Step 4: 8-Hydroxy-5-[methyl(ethylsulfonyl)amino]-1,6-naphthyridine-7-carboxylic acid

Sodium hydroxide (6.73 mL, 6.73 mmol, 1N solution) was added to a suspension of methyl 8-hydroxy-5-[methyl(ethylsulfonyl)amino]-1,6-naphthyridine-7-carboxylate (730 mg, 2.24 mmol) in a 2:1 solution of dioxane/water (20 mL) and the resulting mixture was heated overnight at 55°C overnight. The opaque solution was acidified to a pH = 7 using 1N HCl solution. The reaction was cooled and the solids that had precipitated out of solution were collected by vacuum filtration to give the desired product as an off-white solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 9.21 (1H, dd, *J* = 4.4, 1.6 Hz), 8.62 (1H, dd, *J* = 8.4, 1.5 Hz), 7.93 (1H, dd, *J* = 8.4, 4.2 Hz), 3.50 (2H, q, *J*= 7.5 Hz), 3.32 (3H, s), and 1.30 (3H, t, *J*= 7.5 Hz) ppm.

Step 5: 5-[(Ethylsulfonyl)(methyl)amino]-N-{4-fluoro-2-[(methylamino)-carbonyl]benzyl}-8-hydroxy-1,6-naphthyridine-7-carboxamide



8-Hydroxy-5-[methyl(ethylsulfonyl)amino]-1,6-naphthyridine-7-carboxylic acid was coupled with {2-[(methylamino)carbonyl]-4-fluorophenyl}methanaminium chloride (prepared as described in Example 3). A solution of 8-Hydroxy-5-[methyl(ethylsulfonyl)amino]-1,6-naphthyridine-7-carboxylic acid (50 mg, 0.16 mmol) in dry DMF (15 mL) was stirred at zero degrees. To this was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (40 mg, 0.21 mmol), 1-hydroxy-7-azabenzotriazole (28 mg, 0.21 mmol). The mixture was stirred for 35 minutes at which time the {4-fluoro-2-[(methylamino)carbonyl]phenyl}-methanaminium chloride (38 mg, 0.21 mmol) and diisopropylethylamine (27 mg, 0.21 mmol) was added and the reaction was stirred at room temperature overnight. The reaction was filtered through a glass fiber filter. The filtrate was vacuum reduced and purified by preparative HPLC (Gilson semi preparative HPLC system using a Waters Nova pak column (10x40 mm I.D. cartridges, C18, 6 μM pore size) eluting with 95-5% water (0.025% TFA) / acetonitrile (0.025% TFA) at 35 mL/min). The desired fractions were freeze dried to give the desired product as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.37 (1H, m), 9.19 (1H, m), 8.74 (1H, dd, *J*=8.5, 1.3 Hz), 7.71 (1H, dd, *J* = 8.4, 4.2 Hz), 7.60 (1H, m), 7.18 (1H, s), 7.16 (1H, s), 6.65 (1H, m), 4.63 (2H, d, *J* = 6.5 Hz), 3.43 (2H, q, J= 7.4 Hz), 3.42 (3H, s), 3.04 (3H, d, *J* = 4.7 Hz), and 1.44 (3H, t, *J*= 7.5 Hz) ppm.

LC/MS: calc'd for $C_{21}H_{22}FN_5O_5S$ 475.13, observed MH+ 476.14.

Step 6: Sodium 7-[({2-[(methylamino)carbonyl]-4-fluorobenzyl}amino)carbonyl]- 5-[methyl(ethylsulfonyl)amino]-1,6-naphthyridin-8-olate

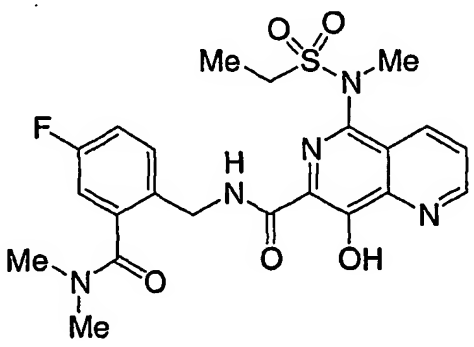
In a manner similar to that described for Example 3, the free acid was converted to the desired salt, that was obtained as a crystalline yellow solid from methanol.

^{1}H NMR (DMSO-d6, 400 MHz) δ 12.26 (1H, m), 8.78 (1H, m), 8.73 (1H, m), 8.23 (1H, dd, J = 8.2, 1.5 Hz), 7.52 (1H, dd, J = 8.4, 4.2 Hz), 7.45 (1H, dd, J = 8.4, 5.7 Hz), 7.23 (1H, dt, J = 8.4, 5.9 Hz), 7.18 (1H, dd, J = 9.3, 2.9 Hz), 4.58 (2H, d, J = 5.9 Hz), 3.51 (2H, q, J= 7.3 Hz), 3.18 (3H, s), 2.81 (3H, d, J= 4.4 Hz), and 1.30 (3H, t, J= 7.5 Hz) ppm.

ES HRMS: calc'd for $C_{21}H_{21}FN_5NaO_5S$ 476.1388, observed 476.1414.

EXAMPLE 26

5-[(Ethylsulfonyl)(methyl)amino]-N-{4-fluoro-2-[(dimethylamino)carbonyl]benzyl}-8-hydroxy-1,6-naphthyridine-7-carboxamide



8-Hydroxy-5-[methyl(ethylsulfonyl)amino]-1,6-naphthyridine-7-carboxylic acid was coupled with {2-[(dimethylamino)carbonyl]-4-fluorophenyl}methanaminium chloride (prepared as described in Example 4). The desired material was prepared in a coupling method identical to that described in Example 25, Step 5.

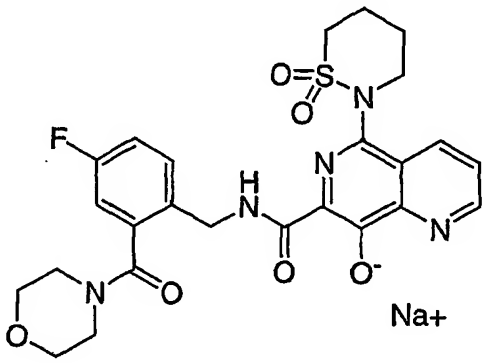
^{1}H NMR ($CDCl_3$, 400 MHz) δ 13.5 (1H, bs), 9.18 (1H, dd, J= 4.2, 1.5 Hz), 8.93 (1H, m), 8.72 (1H, dd, J = 8.5, 1.6 Hz), 7.69 (1H, dd, J = 8.8, 4.2 Hz), 7.53 (1H, dd,

J= 8.4, 5.3 Hz), 7.11 (1H, dt, J= 8.3, 5.7 Hz), 6.98 (1H, dd, J = 8.4, 2.6 Hz), 4.56 (2H, bs), 3.42 (3H, s), 3.41 (2H, q, J= 7.5 Hz), 3.13 (3H, s), 2.98 (3H, s), and 1.41 (3H, t, J= 7.5 Hz) ppm.

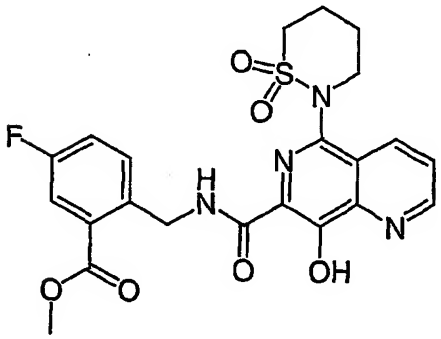
ES HRMS: calc'd for $C_{22}H_{24}FN_5O_5S$ 490.1555, observed 490.1553.

EXAMPLE 27

Sodium 5-(1,1-dioxido-1,2-thiazinan-2-yl)-7-({[4-fluoro-2-(morpholin-4-ylcarbonyl)benzyl]amino}carbonyl)-1,6-naphthyridin-8-olate



Step 1: Methyl 2-[({[5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridin-7-yl]carbonyl}amino)methyl]-5-fluorobenzoate



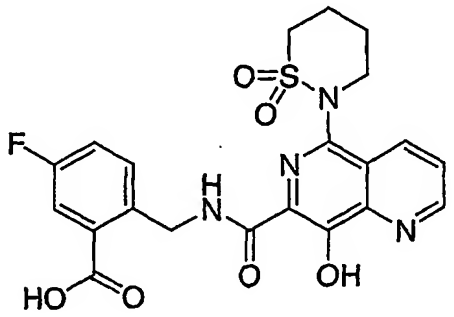
A solution of 5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxylic acid (Example 3, step 7) (1.0g, 3.09 mmol) and HOBT (0.49g, 3.62 mmol) in 10mL DMF was cooled to 0° C and treated with EDC (0.65g, 3.4 mmol). The reaction was stirred for 1 hr and the amount of activated ester formed was monitored by LCMS. After 2 hours an additional 0.2 equivalents of HOBT was

added, followed by methyl 2-(aminomethyl)-5-fluorobenzoate hydrochloride (Example 3C, Step 3) (0.75g, 3.4 mmol) and diisopropylethylamine (0.59 mL, 3.4 mmol). The reaction was allowed to warm to room temperature, evaporated and the residue was partitioned between 10% $KHSO_4$ and $CHCl_3$. The organic layer was dried over Na_2SO_4, filtered, evaporated and the resulting off-white solid was used in the next step. A portion of the material was further purified by reverse-phase chromatography (95:5 water/CH_3CN to 5:95 water/CH_3CN, 0.1% TFA) and lyophilized from dioxane to give the product as a white solid.

^1H NMR ($CDCl_3$, 400 MHz) δ 13.4 (1H, bs), 9.16 (1H, dd, J = 1.8, 4.3 Hz), 9.0 (1H, bt), 8.63 (1H, dd, 1.6, 8.4 Hz), 7.7-7.6 (3H, m), 7.3 (1H, m), 4.8 (2H, dd, J = 2.5, 6.8 Hz) 4.2 (2H, m), 3.95 (3H, s), 3.7 (1H, bd), 3.6 (1H, m), 3.3 (1H, m), 2.5 (3H, m), 1.7 (1H, m) ppm.

Exact mass calc'd for $C_{22}H_{21}FN_4O_6S$ = 499.1239, found 489.1218.

Step 2: 2-[({[5-(1,1-Dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridin-7-yl]carbonyl}amino)methyl]-5-fluorobenzoic acid



To methyl 2-[({[5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridin-7-yl]carbonyl}amino)methyl]-5-fluorobenzoate (800 mg, 1.64 mmol) in 2:1 dioxane /water (5 mL) was added 1 N sodium hydroxide certified solution (4.91 mL, 4.91 mmol) and the reaction was stirred overnight at 50 degrees. The solution was reduced and the aqueous was neutralized with 1 N HCl. The solid that resulted was collected and dried in vacuo to give the desired product.

^1H NMR (DMSO-d6, 400 MHz) δ 13.58 (1H, m), 9.19 (2H, dd, J= 4.0, 1.6 Hz), 8.60 (1H, dd, J=8.6, 1.65 Hz), 7.89 (1H, dd, J = 8.4, 4.2 Hz), 7.71 (1H, dd, J = 9.3, 2.6 Hz), 7.57 (1H, dd, J = 8.8, 5.7 Hz), 7.47 (1H, dt, J = 8.2, 2.7 Hz), 4.86 (2H, bs),

3.87 (1H, bs), 3.82 (1H, bs), 3.48 (1H, buried), 2.33 (2H, m), 2.26 (2H, m), and 1.70 (1H, m) ppm.

ES HRMS: calc'd for $C_{21}H_{19}FN_4O_6S$ 475.1082, observed 475.1071

Step 3: 5-(1,1-Dioxido-1,2-thiazinan-2-yl)-N-[4-fluoro-2-(morpholin-4-ylcarbonyl)benzyl]-8-hydroxy-1,6-naphthyridine-7-carboxamide

To 2-[({[5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridin-7-yl]carbonyl}amino)methyl]-5-fluorobenzoic acid (100 mg, 0.21 mmol) in dry degassed DMF (2 mL) was added morpholine (55 mg, 0.63 mmol) followed by 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (61 mg, 0.32mmol), 1-hydroxy-7-azabenzotriazole (43 mg, 0.32 mmol). The reaction was stirred at room temperature overnight. The solution was filtered through a glass fiber filter. The filtrate was injected directly into the preparative HPLC (Gilson semi preparative HPLC system using a Waters Nova pak column (10x40 mm I.D. cartridges, C18, 6 μM pore size) eluting with 95-5% water (0.025% TFA) / acetonitrile (0.025% TFA) at 35 mL/min). The desired fractions were freeze dried to give the desired product as a white solid.

Step 4: Sodium 5-(1,1-dioxido-1,2-thiazinan-2-yl)-7-({[4-fluoro-2-(morpholin-4-ylcarbonyl)benzyl]amino}carbonyl)-1,6-naphthyridin-8-olate

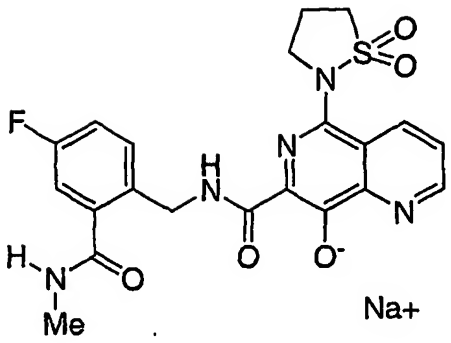
In a manner similar to that described for Example 3, the free acid was converted to the desired salt, that was obtained as a crystalline yellow solid from methanol.

^{1}H NMR (DMSO-d6, 400 MHz) δ 13.66 (1H, s), 9.19 (1H, m), 9.13 (1H, m), 8.60 (1H, d, J = 8.4 Hz), 7.89 (1H, dd, J = 8.0, 3.8 Hz), 7.54 (1H, m), 7.29 (1H, bs), 7.27 (1H, s), 4.8-4.3 (2H, m), 3.84 (2H, bs), 3.7-3.4 (7H, m), 3.26 (2H, bs), 2.30 (4H, m), and 1.68 (1H, bs) ppm.

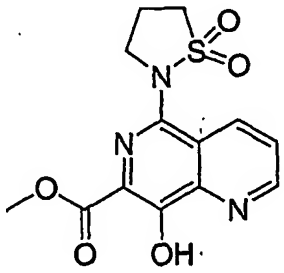
ES HRMS: calc'd for $C_{25}H_{25}FN_5NaO_6S$ 544.1634 observed 544.1639

EXAMPLE 28

Sodium 5-(1,1-dioxidoisothiazolidin-2-yl)-7-[({4-fluoro-2-[(methylamino)-carbonyl]benzyl}amino)carbonyl]-1,6-naphthyridin-8-olate



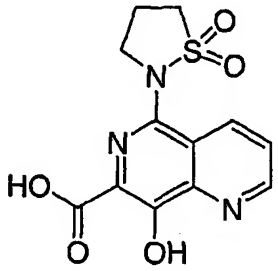
Step 1: Methyl 5-(1,1-dioxidoisothiazolidin-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxylate



In a dried sealable pressure tube flushed with argon was placed 5-Bromo-8-hydroxy-1,6-naphthyridine-7-carboxylic acid methyl ester (1 g, 3.53 mmol), prepared as described in Example 2, Step 1).To this was added isothiazolidine 1,1-dioxide (1.28 g, 10.60 mmol) (prepared following a procedure found in *J. Org. Chem.* 1990, 55(9): 2580-6), dry pyridine (2 mL) and copper(I) oxide (505 mg, 3.53 mmol). The tube was capped and heated to 118° C overnight. The reaction was cooled and filtered through a glass fiber filter, washing with chloroform. The filtrate was reduced and redissolved in chloroform (about 300 mL total volume) and stirred with an EDTA solution (15 g EDTA in 300 mL water) overnight. The aqueous layer became aqua in color and the organic layer became yellow. The layers were separated and the aqueous layer was extracted twice more with chloroform. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was crystallized from methanol to give the desired product as a yellow solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 11.35 (1H, bs) 9.23 (1H, dd, J = 4.0, 1.5 Hz), 8.81 (1H, dd, J = 8.4, 1.5 Hz), 7.95 (1H, dd, J = 8.6, 4.2 Hz), 4.14 (2H, t, J = 6.6 Hz), 3.95 (3H, s), 3.52 (2H, t, J= 7.2 Hz) and 2.56 (2H, m) ppm.

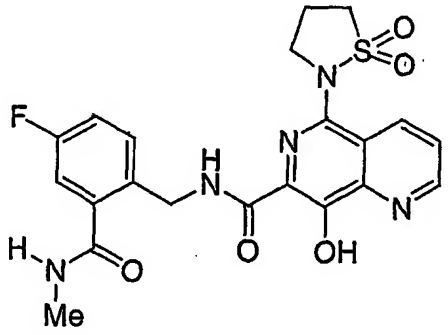
Step 2: 5-(1,1-Dioxidoisothiazolidin-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxylic acid



Sodium hydroxide (4.18 mL, 4.18 mmol, 1N solution) was added to a suspension of methyl 5-(1,1-dioxidoisothiazolidin-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxylate (450 mg, 1.4 mmol) in a 2:1 solution of dioxane/water (10 mL) and the resulting mixture was heated overnight at 55°C overnight. The opaque solution was acidified to a pH = 7 using 1N HCl solution. The reaction was cooled and the solids that had precipitated out of solution were collected by vacuum filtration to give the desired product as an off-white solid.

LC/MS: calc'd for $C_{12}H_{11}N_3O_5S$ calculated mass 309.04 observed MH+ 310.10

Step 3: 5-(1,1-Dioxidoisothiazolidin-2-yl)-N-{4-fluoro-2-[(methylamino)-carbonyl]benzyl}-8-hydroxy-1,6-naphthyridine-7-carboxamide



5-(1,1-Dioxidoisothiazolidin-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxylic acid was coupled with {2-[(methylamino)carbonyl]-4-fluorophenyl}methanaminium chloride (prepared as described in Example 3). A solution of 5-(1,1-dioxidoisothiazolidin-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxylic acid (150 mg, 0.485 mmol) in dry DMF (15 mL) was stirred at zero

degrees. To this was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (121 mg, 0.63 mmol), 1-hydroxy-7-azabenzotriazole (86 mg, 0.63 mmol) and the mixture was stirred for 35 minutes. To this was added {4-fluoro-2-[(methylamino)carbonyl]phenyl}-methanaminium chloride (138 mg, 0.63 mmol) and diisopropylethylamine (81 mg, 0.63 mmol) and the solution was stirred at room temperature overnight. The reaction was filtered through a glass fiber filter. The filtrate was vacuum reduced to a small volume and purified by preparative HPLC (Gilson semi preparative HPLC system using a Waters Nova pak column (10x40 mm I.D. cartridges, C18, 6 μM pore size) eluting with 95-5% water (0.025% TFA) / acetonitrile (0.025% TFA) at 35 mL/min). The desired fractions were freeze dried to give the desired product as a white solid.

LC/MS: calc'd for $C_{21}H_{20}FN_5O_5S$ calculated mass 473.12 observed MH+ 474.09

Step 4: Sodium 5-(1,1-dioxidoisothiazolidin-2-yl)-7-[({4-fluoro-2-[(methylamino)-carbonyl]benzyl}amino)carbonyl]-1,6-naphthyridin-8-olate

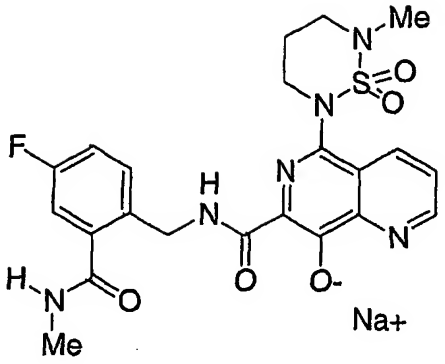
In a manner similar to that described for Example 3, the free base was converted to the desired salt, that was obtained as a crystalline yellow solid from methanol.

^{1}H NMR (DMSO-d6, 400 MHz) δ 8.79 (1H, bs), 8.58 (1H, d, J = 8.4 Hz), 8.52 (1H, m), 7.67 (1H, dd, J = 8.4, 4.4 Hz), 7.43 (1H, bs), 7.3 (1H, bs), 7.17 (1H, d, J = 8.2 Hz), 6.95 (1H, m), 4.51 (2H, m), 4.07 (2H, t, J= 13.2, 6.6 Hz), 3.41 (2H, t, J= 7.3 Hz), 2.77 (3H, d, J= 4.2 Hz), and 2.57 (2H, t, J= 6.8) ppm.

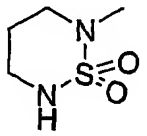
ES HRMS: calc'd for $C_{21}H_{19}FN_5NaO_5S$ 474.1242, observed 474.1218

EXAMPLE 29

Sodium 7-[({4-fluoro-2-[(methylamino)carbonyl]benzyl}amino)carbonyl]-5-(6-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl)-1,6-naphthyridin-8-olate



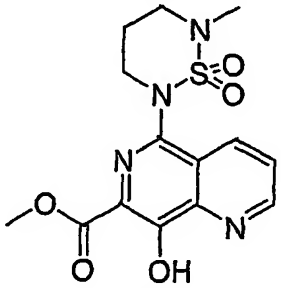
Step 1: 2-Methyl-1,2,6-thiadiazinane 1,1-dioxide



In a dry flask was combined under argon N-methyl-1,3-propanediamine 27.5 gm, 312 mmol) and sulfamide (10 gm, 104 mmol) and the flask was heated overnight to 50 degrees. The amine was removed under reduced pressure to give a gel which was washed with hexane and ether. The residue was chromatographed on silica gel (1 kg) eluting with 50% ethyl acetate and methylene chloride. The colorless band eluting first was collected and reduced to give the desired product as an oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.06 (1H, bs), 3.52 (2H, m), 3.30 (2H, t, J=5.7 Hz), 2.76 (3H, s), and 1.79 (2H, m).

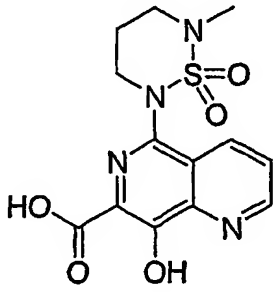
Step 2: Methyl 8-hydroxy-5-(6-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl)-1,6-naphthyridine-7-carboxylate



In a dried sealable pressure tube flushed with argon was placed methyl 5-bromo-1,6-naphthyridine-7-carboxylate (0.6gms, 2.12 mmol), prepared as described in Example 2, Step 1, 2-Methyl-1,2,6-thiadiazinane 1,1-dioxide (955 mg, 6.36 mmol), dry pyridine (2 mL) and copper(I) oxide (303 mg, 2.12 mmol). The tube was capped and heated to 118°C overnight. The reaction was cooled and filtered through a glass fiber filter, washing with chloroform. The filtrate was diluted with chloroform (about 300 mL total volume) and stirred with an EDTA solution (15 g EDTA in 300 mL water) for two hours or until the aqueous layer became aqua in color and the organic layer became yellow. The layers were separated and the aqueous layer was extracted twice more with chloroform. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue crystallized from a small amount of methanol and was filtered and washed with methanol and dried *in vacuo* to give the desired product as a pale yellow solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.75 (1H, s), 9.18 (1H, dt, J = 4.2, 1.6 Hz), 8.69 (1H, dt, J = 8.5, 1.5 Hz), 7.70 (1H, m), 4.12 (2H, m), 4.08 (3H, s), 3.80 (2H, m) and 2.95 (3H, s), 1.5(2H, buried) ppm.

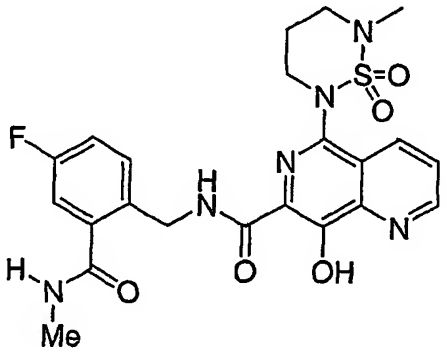
Step 3: 8-Hydroxy-5-(6-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl)-1,6-naphthyridine-7-carboxylic acid



Sodium hydroxide (3.85 mL, 3.85 mmol, 1N solution) was added to a suspension of methyl 8-hydroxy-5-(6-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl)-1,6-naphthyridine-7-carboxylate (452 mg, 1.28 mmol) in a 2:1 solution of dioxane/water (10 mL) and the resulting mixture was heated overnight at 55°C overnight. The opaque solution was acidified to a pH = 7 using 1N HCl solution. The reaction was cooled and the solids that had precipitated out of solution were collected by vacuum filtration to give the desired product as an off-white solid.

^{1}H NMR (DMSO-d6, 400 MHz) δ 9.19 (1H, dd, J= 4.2, 1.5 Hz), 8.64 (1H, dd, J=8.4, 1.5 Hz), 7.91 (1H, dd, *J* = 8.6, 4.2 Hz), 4.0 (2H, m), 3.70 (2H, t, *J* = 5.7 Hz), 2.97 (3H, s), 2.4-2.0 (2H, m) ppm.

Step 4: N-{4-Fluoro-2-[(methylamino)carbonyl]benzyl}-8-hydroxy-5-(6-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl)-1,6-naphthyridine-7-carboxamide



8-Hydroxy-5-(6-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl)-1,6-naphthyridine-7-carboxylic acid was coupled with {2-[(methylamino)carbonyl]-4-fluorophenyl}methanaminium chloride (prepared as described in Example 3). A solution of 8-hydroxy-5-(6-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl)-1,6-naphthyridine-7-carboxylic acid (200mg, 0.59 mmol) in dry DMF (2 mL) was stirred at zero degrees. To this was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (147 mg, 0.77mmol), 1-hydroxy-7-azabenzotriazole (181 mg, 1.18 mmol). The mixture was stirred for 35 minutes at which time the {4-fluoro-2-[(methylamino)carbonyl]phenyl}-methanaminium chloride (194 mg, 0.89 mmol) and diisopropylethylamine (124 μL, 0.7 mmol) was added and the reaction was stirred at room temperature for 1 hour. The reaction was filtered through a glass fiber filter. The filtrate was injected directly into the preparative HPLC (Gilson semi preparative HPLC system using a Waters Nova pak column (10x40 mm I.D. cartridges, C18, 6 μM pore size) eluting with 95-5% water (0.025% TFA) / acetonitrile (0.025% TFA) at 35 mL/min). The desired fractions were freeze dried to give the desired product as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 13.4 (1H, bs), 9.15 (2H, dd, J= 4.2, 1.5 Hz), 9.10 (1H, m), 8.60 (1H, dd, J=8.6, 1.6 Hz), 7.65 (1H, dd, *J* = 8.4, 4.2 Hz), 7.60 (1H, dd, *J* =

7.9, 5.5 Hz), 7.26 (1H, m), 6.18 (1H, m), 4.68 (2H, d, J= 6.6 Hz), 4.68 (2H, d, J = 6.6 Hz), 4.10 (2H, bs), 3.8 (2H, bs), 3.03 (3H, dd, J=4.9, 1.8 Hz) and 2.95 (3H, d, J=1.6) ppm.

LC/MS: calc'd for $C_{22}H_{23}FN_6O_5S$ calculated mass 502.14 observed MH+ 503.14

Step 5: Sodium 7-[({4-fluoro-2-[(methylamino)carbonyl]benzyl}amino)-carbonyl]-5-(6-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl)-1,6-naphthyridin-8-olate

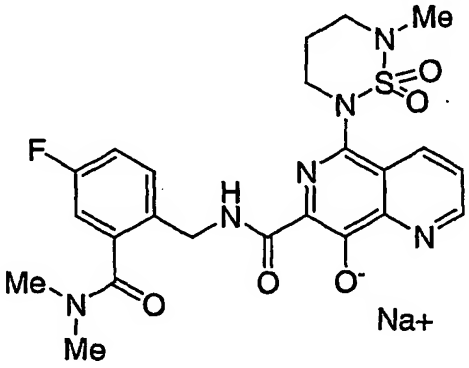
In a manner similar to that described for Example 3, the free acid was converted to the desired salt, that was obtained as a crystalline yellow solid from methanol.

^{1}H NMR (DMSO-d6, 400 MHz) δ 12.40 (1H, bs), 8.77 (2H, m), 8.30 (1H, d, J = 8.1 Hz), 7.50 (2H, m), 7.20 (2H, t, J = 11.2 Hz), 4.58 (2H, d, J = 5.4 Hz), 3.91 (1H, bs), 3.72 (1H, bs), 3.60 (2H, m), 2.96 (3H, s), 2.81 (3H, dd, J= 4.4, 1.8 Hz), 2.5 (1H, buried) and 1.82 (1H, m) ppm.

ES HRMS: calc'd for C22H22FN6NaO5S 503.1507, observed 503.1510.

EXAMPLE 30

Sodium 7-[({2-[(dimethylamino)carbonyl]-4-fluorobenzyl}amino)carbonyl]-5-(6-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl)-1,6-naphthyridin-8-olate



Step 1: N-{2-[(dimethylamino)carbonyl]-4-fluorobenzyl}-8-hydroxy-5-(6-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl)-1,6-naphthyridine-7-carboxamide

8-Hydroxy-5-(6-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl)-1,6-naphthyridine-7-carboxylic acid was coupled with {2-[(dimethylamino)carbonyl]-4-

fluorophenyl}methanaminium chloride (prepared as described in Example 3). A solution of 8-Hydroxy-5-(6-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl)-1,6-naphthyridine-7-carboxylic acid (200mg, 0.59 mmol) in dry DMF (2 mL) was stirred at zero degrees. To this was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (147 mg, 0.77mmol), 1-hydroxy-7-azabenzotriazole (118 mg, 0.768 mmol). The mixture was stirred for 35 minutes at which time the {4-fluoro-2-[(dimethylamino)carbonyl]phenyl}-methanaminium chloride (206 mg, 0.89 mmol) and diisopropylethylamine (90 mg, 0.7 mmol) was added and the reaction was stirred at room temperature for 1 hour. The reaction was filtered through a glass fiber filter. The filtrate was injected directly into the preparative HPLC (Gilson semi preparative HPLC system using a Waters Nova pak column (10x40 mm I.D. cartridges, C18, 6 μM pore size) eluting with 95-5% water (0.025% TFA) / acetonitrile (0.025% TFA) at 35 mL/min). The desired fractions were freeze dried to give the desired product as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 13.38 (1H, bs), 9.15 (1H, m), 8.65 (2H, dt, J=8.4,1.6 Hz), 7.65 (1H, dd, *J* = 8.6, 4.2 Hz), 7.55 (1H, dd, *J* = 8.6, 5.5 Hz), 7.52 (1H, s), 7.10 (1H, dt, J=8.2, 2.6 Hz), 6.96 (1H, dd, J=8.2, 2.6 Hz), 4.64 (2H, d, m), 4.10 (1H, m), 3.76 (1H, t, *J*= 5.9 Hz), 3.13 (3H, s), and 2.96 (3H, s), 2.95 (3H, s), 2.8 (1H, bs), 2.0 (1H, bs) ppm.

Step 2: Sodium 7-[({4-fluoro-2-[(dimethylamino)carbonyl]benzyl}amino)-carbonyl]-5-(6-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl)-1,6-naphthyridin-8-olate

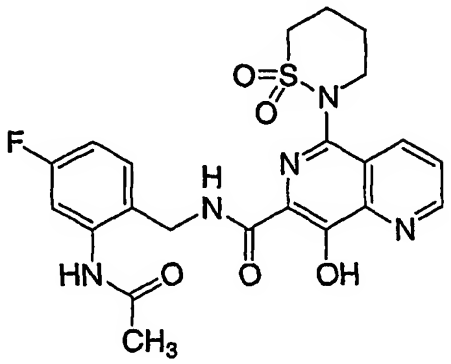
In a manner similar to that described for Example 3, the free acid was converted to the desired salt, that was obtained as a crystalline yellow solid from methanol.

^{1}H NMR (DMSO-d6, 400 MHz) δ 12.2 (1H, bs), 8.76 (1H, m), 8.31 (1H, d, *J* = 8.2 Hz), 7.52 (1H, dd, J=8.0, 4.0 Hz), 7.47(1H, dd, *J* = 8.4, 5.7 Hz), 7.20 (1H, dt, *J* = 8.7, 2.4 Hz), 7.09(1H, dd, *J* = 8.8, 2.6 Hz), 4.42 (2H, d, J=5.5 Hz), 4.10 (1H, m), 3.86 (1H, bs), 3.70(1H, bs), 3.64 (2H, t, J=5.5), 3.01 (3H, s), 2.96 (3H, s), 2.78 (3H, s), 2.5 (1H, buried), and 1.85 (1H, bs) ppm.

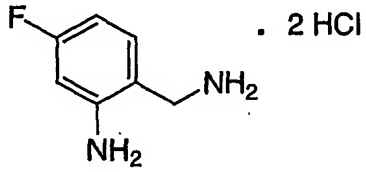
ES HRMS: calc'd for $C_{23}H_{24}FN_6NaO_5S$ 517.1664, observed 517.1655.

EXAMPLE 31

N-[2-(acetylamino)-4-fluorobenzyl]-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide

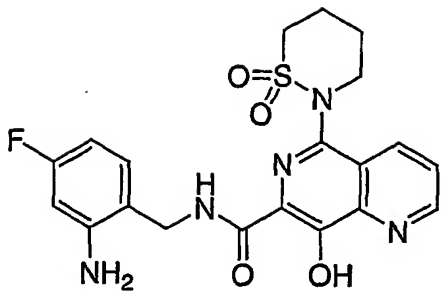


Step 1: 2-amino-4-fluorobenzylamine bis-hydrochloride



A solution of 4-fluoro-2-nitrobenzonitrile (1g, 6.02 mmol) in ethanol (about 10 to 50 mL) is hydrogenated and shaken overnight in the presence of 10% Pd/C (about 0.2 to 0.5g) in a Parr apparatus (about 10 to 60 psig H_2) at a temperature of about 25 to about 60°C. The resulting solution is filtered and evaporated to give crude 2-amino-4-fluorobenzonitrile, which is treated with neat acetic anhydride (about 16 mL) overnight. A further portion of acetic anhydride (about 16 mL) is added the following day, and the resulting solution is hydrogenated overnight in the presence of 10% Pd/C (about 0.2 - 0.5g) in a Parr apparatus (about 3 - 60 psig H_2). The solution is filtered to give crude N,N'-diacetyl-2-amino-4-fluorobenzylamine, which is heated to reflux in 6N HCl (about 30mL) for about 30 minutes and then evaporated to give the title di-HCl salt.

Step 2: N-(2-amino-4-fluorobenzyl)-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide



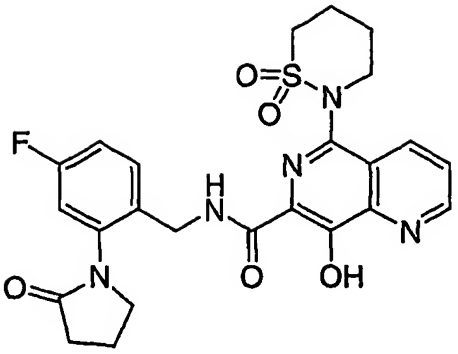
Diisopropylamine (about 2-4 equivalents) is added to a solution of the title product of Step 1 (0.34 g, 2.46 mmol) in dry MeOH (about 15 mL) followed by 5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxylic acid methyl ester (about 0.6 - 1 equivalent). The resulting mixture is heated (about 60 - 80°C) overnight with stirring, then cooled to room temperature (about 20 -25°C), and partitioned between methylene chloride and 0.1 N aqueous HCl. The organic layer is washed with water and brine, dried and concentrated to give crude title product.

Step 3: N-[2-(acetylamino)-4-fluorobenzyl]-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide

Acetyl chloride (about 2 - 3 equivalents) is slowly added at low temperature (about 0°C) to a solution of the title product of Step 2 (0.11 g, 0.25 mmol) and triethylamine (about 2 - 3 equivalents) in methylene chloride (about 10 mL). The resulting mixture is stirred for about 30 minutes and then partitioned between methylene chloride and 0.1 N aqueous HCl. The organic layer is washed with water and brine, dried and concentrated to give a diacetylated intermediate, which is then treated with 0.5N NaOMe in MeOH with stirring for about 30 minutes. The treated mixture is then partitioned between methylene chloride and 0.1 N aqueous HCl, and the organic layer is washed with water and brine, dried and concentrated to give crude title product which is recrystallized with MeOH.

EXAMPLE 32

5-(1,1-dioxido-1,2-thiazinan-2-yl)-N-[4-fluoro-2-(2-oxopyrrolidin-1-yl)benzyl]-8-hydroxy-1,6-naphthyridine-7-carboxamide



4-Chlorobutanoyl chloride (about 2 - 3 equivalents) is slowly added at low temperature (about 0°C) to a solution of N-(2-amino-4-fluorobenzyl)-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide (0.15 g, 0.34 mmol) and triethylamine (about 2 - 3 equivalents) in methylene chloride (about 10 mL). The resulting mixture is then stirred for about 30 minutes and partitioned between methylene chloride and 0.1 N aqueous HCl, after which the organic layer is washed with water and brine, dried and concentrated to give impure 7-[({2-[(4-chlorobutanoyl)amino]-4-fluorobenzyl}amino)carbonyl]-5-(1,1-dioxido-1,2-thiazinan-2-yl)-1,6-naphthyridin-8-yl 4-chlorobutanoate. This material is then dissolved in about 2 mL DMF and is slowly added at low temperature (about 0°C) to a suspension of NaH (60% dispersion in oil, 2.5-4 equivalents) in DMF. The resulting mixture is stirred for about 30 minutes and then warmed to room temperature for about 2 hours, after which ice is added and the mixture partitioned between methylene chloride and 0.1 N aqueous HCl. The organic layer is washed with water and brine, dried and concentrated to give a precipitate that is dissolved in methylene chloride (about 5 mL) and treated with 0.5 N NaOMe in MeOH (about 2 - 3 equivalents), the mixture stirred for about 30 minutes, and then partitioned between methylene chloride and 0.1 N aqueous HCl. The organic layer is washed with water and brine, dried and concentrated to give crude title product which is recrystallized with MeOH.

EXAMPLE 33

Oral Compositions

As a specific embodiment of an oral composition of a compound of this invention, 50 mg of compound of Example 3 is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0 hard gelatin

capsule. Encapsulated oral compositions containing any one of the compounds of Examples 3C and 4-30 can be similarly prepared.

EXAMPLE 34

HIV Integrase Assay: Strand Transfer Catalyzed by Recombinant Integrase

Assays for the strand transfer activity of integrase were conducted in accordance with the method described in Example 193 of WO 02/30930 for recombinant integrase. Representative compounds of the present invention exhibit inhibition of strand transfer activity in this assay. For example, the compounds prepared in Examples 3, 3C and 4-30 were tested in the integrase assay and all were found to have IC_{50}'s less than 0.5 micromolar.

Further description on conducting the assay using preassembled complexes is found in Wolfe, A.L. et al., *J. Virol.* 1996, 70: 1424-1432, Hazuda et al., *J. Virol.* 1997, 71: 7005-7011; Hazuda et al., *Drug Design and Discovery* 1997, 15: 17-24; and Hazuda et al., *Science* 2000, 287: 646-650.

EXAMPLE 35

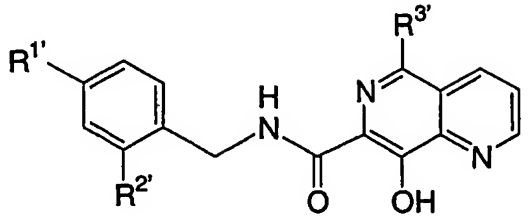
Assay for inhibition of HIV replication

Assays for the inhibition of acute HIV infection of T-lymphoid cells were conducted in accordance with Vacca, J.P. et al., *Proc. Natl. Acad. Sci. USA* 1994, 91: 4096. Representative compounds of the present invention exhibit inhibition of HIV replication in this assay. For example, the compounds prepared in Examples 3, 3C and 4-30 were tested in the present assay and all were found to have IC_{95}'s less than 5 micromolar.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, the practice of the invention encompasses all of the usual variations, adaptations and/or modifications that come within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A compound of Formula (II):



(II),

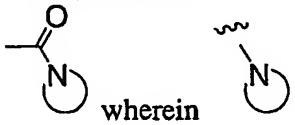
wherein

$R^{1'}$ is -H or -F;

$R^{2'}$ is

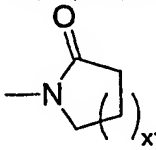
(1) $-C_{1-6}$ alkyl-C(=O)N(R^aR^b),

(2) -C(=O)N(R^aR^b),

(3)  wherein is azetidinyl, pyrrolidinyl, piperidinyl, or morpholino,

(4) triazolyl or tetrazolyl,

(5) -N(R^a)-C(R^b)=O,

(6)  wherein x1 is an integer equal to zero, 1, or 2, or

(7) $-CO_2R^c$;

$R^{3'}$ is:

(1) -H,

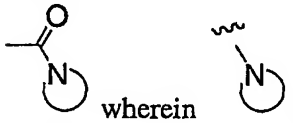
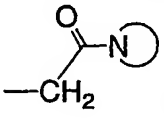
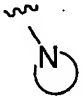
(2) -C(=O)N(R^aR^b),

(3) $-CH_2$-C(=O)N(R^aR^b),

(4) $-CH_2CH_2$-C(=O)N(R^aR^b),

(5) $-S-CH_2$-C(=O)N(R^aR^b),

(6) $-O-CH_2$-C(=O)N(R^aR^b),

(7) -N(R^a)-C(R^b)=O,
(8) -N(SO_2R^c)-CH_2-C(=O)N(R^aR^b),
(9) -N(R^a)-C(=O)-C(=O)-N(R^aR^b),
(10) -N(R^a)SO_2R^c,
(11) -CH=CH-C(=O)-N(R^aR^b),
(12) -N(R^a)-CH_2-C(=O)N(R^aR^b),
(13) -N(R^a)-C(=O)-N(R^aR^b),
(14) -HetC',
(15) -$(CH_2)_{1-3}$ alkyl-HetC',
(16) -N(R^a)-$(CH_2)_{1-3}$-HetC',
(17) -N(R^a)-SO_2-N(R^aR^b),
(18) -HetQ',
(19)  wherein is as defined above in $R^{2'}$, or
(20)  wherein  is as defined above in $R^{2'}$;

HetC' is a 5- to 7-membered saturated heterocyclic ring containing from 1 to 4 heteratoms independently selected from N, O and S, wherein the saturated heterocyclic ring is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-4} alkyl, -C_{3-6} cycloalkyl, -O-C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} haloalkyl, -CN, oxo, phenyl, benzyl, phenylethyl, -$(CH_2)_{0-3}$C(=O)N(R^aR^b), -$(CH_2)_{0-3}$C(=O)R^a, -N(R^a)-C(=O)R^b, -N(R^a)-CO_2R^b, -$(CH_2)_{1-3}$N(R^a)-C(=O)R^b, -N(R^aR^b), -$(CH_2)_{1-3}$N(R^aR^b), -SO_2R^c, -$(CH_2)_{0-3}$C(=O)-HetD', -HetD', -N(R^a)-HetD', and -$(CH_2)_{1-3}$-HetD'; wherein each HetD' is independently a 5- or 6-membered heteroaromatic ring containing from 1 to 4 nitrogen atoms or a 5- or 6-membered saturated heterocyclic ring containing from 1 to 4 nitrogen atoms, wherein the ring is optionally substituted with 1 or 2 substituents each of which is independently halogen, oxo, -C_{1-4} alkyl, or -O-C_{1-4} alkyl;

HetQ' is a 7- to 9-membered bridged azabicycloalkyl saturated ring system containing a C_{5-7} azacycloalkyl ring in which two of the ring carbons are connected by a bridge containing 1 or 2 carbon atoms; wherein the bridged azabicycloalkyl ring system is

optionally substituted with from 1 to 4 substituents each of which is independently halogen, oxo, or -C_{1-4} alkyl;

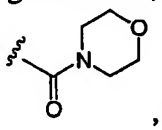
each R^a is independently -H, -C_{1-6} alkyl, or -C_{3-6} cycloalkyl;

each R^b is independently -H, -C_{1-6} alkyl, or -C_{3-6} cycloalkyl; and

each R^c is independently a -C_{1-6} alkyl or -C_{3-6} cycloalkyl;

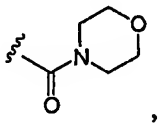
or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, wherein $R^{2'}$ is

-$(CH_2)_{1-3}$-C(=O)N(R^aR^b), -C(=O)N(R^aR^b),  , triazolyl, or tetrazolyl;

or a pharmaceutically acceptable salt thereof.

3. The compound according to claim 2, wherein

$R^{2'}$ is -$(CH_2)_{1-3}$-C(=O)N($R^{a*}R^{b*}$), -C(=O)N($R^{a*}R^{b*}$),  , triazolyl, or tetrazolyl;

R^{a*} and R^{b*} are each independently -H, -C_{1-4} alkyl, or cyclopropyl, with the proviso that R^{a*} and R^{b*} are not both -H;

each R^a in $R^{3'}$ is independently -H, -C_{1-4} alkyl, or cyclopropyl;

each R^b in $R^{3'}$ is independently -H, -C_{1-4} alkyl, or cyclopropyl; and

each R^c in $R^{3'}$ is independently a -C_{1-4} alkyl or cyclopropyl;

or a pharmaceutically acceptable salt thereof.

4. The compound according to claim 3, wherein $R^{2'}$ is $-(CH_2)_{1-3}-C(=O)N(R^{a*}R^{b*})$ or $-C(=O)N(R^{a*}R^{b*})$; and

one of R^{a*} and R^{b*} is -H, and the other of R^{a*} and R^{b*} is $-C_{1-4}$ alkyl or cyclopropyl;

or a pharmaceutically acceptable salt thereof.

5. The compound according to any one of claims 1 to 4, wherein

HetC' in the definition of $R^{3'}$ is a saturated heterocyclic ring selected from piperidinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, isothiazolidinyl, oxazolidinyl, isooxazolidinyl, pyrrolidinyl, imidazolidinyl, piperazinyl, tetrahydrofuranyl, pyrazolidinyl, hexahydropyrimidinyl, thiazinanyl, thiazepanyl, thiadiazepanyl, dithiazepanyl, diazepanyl, and thiadiazinanyl, wherein the saturated heterocyclic ring is unsubstituted or substituted with 1 to 4 substituents each of which is independently:

(a) methyl or ethyl,
(b) =O,
(c) $-C(=O)N(R^aR^b)$,
(d) $-CH_2C(=O)N(R^aR^b)$,
(e) $-C(=O)R^a$, or
(f) $-SO_2R^c$;

or a pharmaceutically acceptable salt thereof.

6. The compound according to any one of claims 1 to 5, wherein $R^{3'}$ is -H, $-C(=O)N(R^aR^b)$, $-N(R^a)SO_2R^c$, $-N(R^a)-C(=O)-C(=O)-N(R^aR^b)$, 1,1-dioxido-1,2-thiazinan-2-yl, 1,1-dioxidoisothiazolidin-2-yl, 1,1-dioxido-1,2,6-thiadiazinan-2-yl, 6-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl, or 3-oxo-2-azabicyclo[2.2.1]hept-2-yl;

or a pharmaceutically acceptable salt thereof.

7. The compound according to claim 1, wherein:

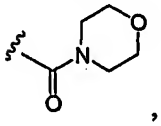
$R^{1'}$ is -H or -F;

$R^{2'}$ is

(1) $-(CH_2)_{1-3}-C(=O)N(R^{a*}R^{b*})$,

(2) $-C(=O)N(R^{a*}R^{b*})$,

(3) $-C(=O)NH_2$,

(4)  ,

(5) triazolyl, or

(6) tetrazolyl;

$R^{3'}$ is:

(1) -H,

(2) $-C(=O)N(R^{a"}R^{b"})$,

(3) $-CH_2-C(=O)N(R^{a"}R^{b"})$,

(4) $-CH_2CH_2-C(=O)N(R^{a"}R^{b"})$,

(5) $-N(R^a)-C(R^b)=O$,

(6) $-N(R^a)-C(=O)-C(=O)-N(R^aR^b)$,

(7) $-N(R^a)SO_2R^c$,

(8) -HetC', or

(9) -HetQ';

HetC' is a saturated heterocyclic ring selected from thiazinanyl, isothiazolidinyl, and thiadiazinanyl, wherein the saturated heterocyclic ring is optionally substituted with from 1 to 4 substituents each of which is independently $-C_{1-4}$ alkyl or oxo;

HetQ' is azabicyclo[2.2.1]heptyl optionally substituted with 1 or 2 substituents each of which is independently oxo or $-C_{1-4}$ alkyl;

one of R^{a*} and R^{b*} is -H, $-C_{1-4}$ alkyl, or cyclopropyl, and the other of R^{a*} and R^{b*} is $-C_{1-4}$ alkyl or cyclopropyl;

each of $R^{a"}$ and $R^{b"}$ is independently $-C_{1-4}$ alkyl or cyclopropyl;

each of R^a and R^b is independently -H, -C_{1-4} alkyl, or cyclopropyl; and

R^c is -C_{1-4} alkyl or cyclopropyl;

or a pharmaceutically acceptable salt thereof.

8. The compound according to claim 7, wherein

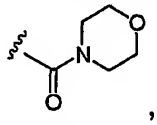
$R^{1'}$ is -H or -F;

$R^{2'}$ is:

(1) -$CH_2C(=O)N(R^{a*}R^{b*})$,

(2) -$C(=O)N(R^{a*}R^{b*})$,

(3) -$C(=O)NH_2$,

(4)  ,

(5) triazolyl, or

(6) tetrazolyl;

$R^{3'}$ is:

(1) -$C(=O)N(R^{a''}R^{b''})$,

(2) -CH_2-$C(=O)N(R^{a''}R^{b''})$,

(3) -CH_2CH_2-$C(=O)N(R^{a''}R^{b''})$,

(4) -$N(R^a)$-$C(R^b)=O$,

(5) -$N(R^a)$-$C(=O)$-$C(=O)$-$N(R^aR^b)$,

(6) -$N(R^a)SO_2R^c$,

(7) 1,1-dioxido-1,2-thiazinan-2-yl,

(8) 1,1-dioxidoisothiazolidin-2-yl,

(9) 1,1-dioxido-1,2,6-thiadiazinan-2-yl,

(10) 6-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl, or

(11) 3-oxo-2-azabicyclo[2.2.1]hept-2-yl;

one R^{a*} and R^{b*} is -H, -C_{1-3} alkyl, or cyclopropyl, and the other of R^{a*} and R^{b*} is -C_{1-3} alkyl;

each of $R^{a''}$ and $R^{b''}$ is independently a -C_{1-3} alkyl;

each of R^{a} and R^{b} is independently a -C_{1-3} alkyl; and

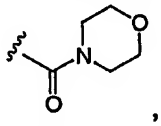
R^{c} is -C_{1-3} alkyl;

or a pharmaceutically acceptable salt thereof.

9. The compound according to claim 8, wherein

$R^{1'}$ is -H or -F;

$R^{2'}$ is:

(1) -$CH_2C(=O)NH(CH_3)$,
(2) -$CH_2C(=O)N(CH_3)_2$,
(3) -$C(=O)NH(CH_3)$,
(4) -$C(=O)N(CH_3)_2$,
(5) -$C(=O)NH(CH_2CH_3)$,
(6) -$C(=O)NH(CH_2CH_2CH_3)$,
(7) -$C(=O)NH(CH(CH_3)_2)$,
(8) -$CH_2C(=O)NH$(cyclopropyl),
(9) -$C(=O)NH_2$,
(10)  ,
(11) triazolyl, or
(12) tetrazolyl; and

$R^{3'}$ is:

(1) -$C(=O)N(CH_3)_2$,
(2) -$N(CH_3)$-$C(CH_3)$=O,

(3) $-N(CH_3)-C(=O)-C(=O)-N(CH_3)_2$,
(4) $-N(CH_3)SO_2CH_3$,
(5) $-N(CH_3)SO_2CH_2CH_3$,
(6) $-N(CH_2CH_3)SO_2CH_3$,
(7) 1,1-dioxido-1,2-thiazinan-2-yl,
(8) 1,1-dioxidoisothiazolidin-2-yl,
(9) 6-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl, or
(10) 3-oxo-2-azabicyclo[2.2.1]hept-2-yl;

provided that:

(i) when $R^{3'}$ is $-C(=O)N(CH_3)_2$, then $R^{2'}$ is not $-C(=O)NH_2$; and
(ii) when $R^{3'}$ is $-N(CH_3)-C(CH_3)=O$ or $-N(CH_3)-C(=O)-C(=O)-N(CH_3)_2$, then $R^{2'}$ is not $-C(=O)N(CH_3)_2$ or $-CH_2C(=O)N(CH_3)_2$;

or a pharmaceutically acceptable salt thereof.

10. The compound according to claim 9, wherein:

$R^{2'}$ is $-C(=O)NH_2$, $-C(=O)NH(CH_3)$, $-C(=O)N(CH_3)_2$, or $-C(=O)NH(CH_2CH_3)$; and

$R^{3'}$ is $-N(CH_3)SO_2CH_3$, $-N(CH_3)SO_2CH_2CH_3$, 1,1-dioxido-1,2-thiazinan-2-yl, or 6-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl;

or a pharmaceutically acceptable salt thereof.

11. A compound selected from the group consisting of:

N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{2-[(dimethylamino)carbonyl]-4-fluorobenzyl}-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{2-[2-(dimethylamino)-2-oxoethyl]benzyl}-5- (1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{2-[2-(methylamino)-2-oxoethyl]benzyl}-5-(1,1-Dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{2-[(dimethylamino)carbonyl]-4-fluorobenzyl}-5-[methyl(methylsulfonyl)amino]-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-5-[methyl(methylsulfonyl)amino]-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{2-[(dimethylamino)carbonyl]-4-fluorobenzyl}-5-[(dimethylamino)carbonyl]-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-5-[(dimethylamino)carbonyl]-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{2-[2-(dimethylamino)-2-oxoethyl]-4-fluorobenzyl}-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

5-(1,1-dioxido-1,2-thiazinan-2-yl)-N-{4-fluoro-2-[2-(methylamino)-2-oxoethyl]benzyl}-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{2-[(dimethylamino)carbonyl]-4-fluorobenzyl}-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{2-[(dimethylamino)carbonyl]-4-fluorobenzyl}-5-[ethyl(methylsulfonyl)amino]-8-hydroxy-1,6-naphthyridine-7-carboxamide;

5-[ethyl(methylsulfonyl)amino]-N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{2-[(dimethylamino)carbonyl]benzyl}-8-hydroxy-5-[methyl(methylsulfonyl)amino]-1,6-naphthyridine-7-carboxamide;

8-hydroxy-N-{2-[(methylamino)carbonyl]benzyl}-5-[methyl(methylsulfonyl)amino]-1,6-naphthyridine-7-carboxamide;

N-[2-(aminocarbonyl)-4-fluorobenzyl]-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{2-[(cyclopropylamino)carbonyl]-4-fluorobenzyl}-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

5-(1,1-dioxido-1,2-thiazinan-2-yl)-N-[4-fluoro-2-(morpholin-4-ylcarbonyl)benzyl]-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{2-[(dimethylamino)carbonyl]benzyl}-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-N-{2-[(methylamino)carbonyl]benzyl}-1,6-naphthyridine-7-carboxamide;

N-7-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-8-hydroxy-N-5-isopropyl-N-5-methyl-1,6-naphthyridine-5,7-dicarboxamide;

N-1-{7-[({4-fluoro-2-[(methylamino)carbonyl]benzyl}amino)carbonyl]-8-hydroxy-1,6-naphthyridin-5-yl}-N-1-,N-2,N-2-trimethylethanediamide;

5-[acetyl(methyl)amino]-N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{4-fluoro-2-[(isopropylamino)carbonyl]benzyl}-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{4-fluoro-2-[(ethylamino)carbonyl]benzyl}-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{4-fluoro-2-[(n-propylamino)carbonyl]benzyl}-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{4-fluoro-2-[(amino)carbonyl]benzyl}-5-[methyl(methylsulfonyl)amino]-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{4-fluoro-2-[(ethylamino)carbonyl]benzyl}-5-[methyl(methylsulfonyl)amino]-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-[2-(1H-1,2,4-triazol-1-yl)benzyl]-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-[2-(1H-1,2,4-tetrazol-1-yl)benzyl]-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-8-hydroxy-5-[(1R,4S)-3-oxo-2-azabicyclo[2.2.1]hept-2-yl]-1,6-naphthyridine-7-carboxamide;

N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-8-hydroxy-5-[(1S,4R)-3-oxo-2-azabicyclo[2.2.1]hept-2-yl]-1,6-naphthyridine-7-carboxamide;

N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-5-[(ethylsulfonyl)(methyl)amino]-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{4-fluoro-2-[(dimethylamino)carbonyl]benzyl}-5-[(ethylsulfonyl)(methyl)amino]-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-5-(1,1-dioxidoisothiazolidin-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-5-(6-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{4-fluoro-2-[(dimethylamino)carbonyl]benzyl}-5-(6-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-[2-(acetylamino)-4-fluorobenzyl]-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

5-(1,1-dioxido-1,2-thiazinan-2-yl)-N-[4-fluoro-2-(2-oxopyrrolidin-1-yl)benzyl]-8-hydroxy-1,6-naphthyridine-7-carboxamide

and pharmaceutically acceptable salts thereof.

12. The compound according to claim 11, which is a compound selected from the group consisting of:

N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{2-[(dimethylamino)carbonyl]-4-fluorobenzyl}-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-5-[methyl(methylsulfonyl)amino]-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{4-fluoro-2-[(ethylamino)carbonyl]benzyl}-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-[2-(aminocarbonyl)-4-fluorobenzyl]-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide:

N-{4-fluoro-2-[(amino)carbonyl]benzyl}-5-[methyl(methylsulfonyl)amino]-8-hydroxy-1,6-naphthyridine-7-carboxamide;

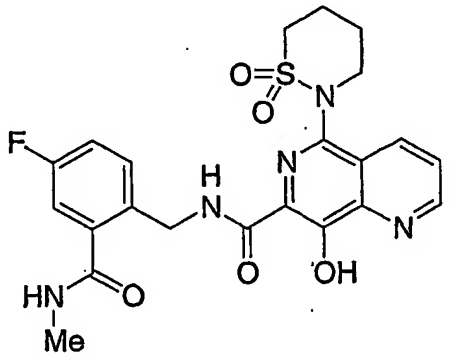
5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-N-{2-[(methylamino)carbonyl]benzyl}-1,6-naphthyridine-7-carboxamide:

N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-5-[(ethylsulfonyl)(methyl)amino]-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-5-(6-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

and pharmaceutically acceptable salts thereof.

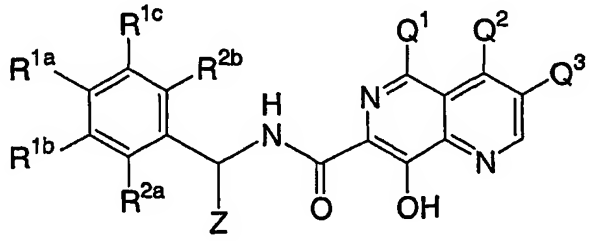
13. The compound according to claim 12, which is N-{4-fluoro-2-[(methylamino)carbonyl]benzyl}-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide,having the formula:



;

or a pharmaceutically acceptable salt thereof.

14. A compound of Formula (III):



(III),

wherein

R^{1a}, R^{1b}, and R^{1c} are each independently -H, halogen, -C_{1-6} alkyl, -C_{3-6} cycloalkyl, or -C_{1-6} haloalkyl;

R^{2a} and R^{2b} are each independently:

(1) -H,

(2) -C_{1-6} alkyl substituted with from 1 to 3 substituents each of which is independently -CN, -NO_2, -OCO_2R^c, -$S(=O)R^c$, -SO_2R^c, -$SO_2N(R^aR^b)$, -$N(R^a)CO_2R^c$, -$N(R^a)SO_2R^c$, -$N(R^a)SO_2N(R^aR^b)$, -$OC(=O)N(R^aR^b)$, or -$N(R^a)C(=O)N(R^aR^b)$;

(3) -O-C_{1-6} alkyl substituted with from 1 to 3 substituents each of which is independently -$S(=O)R^c$, -SO_2R^c, -$C(=O)N(R^aR^b)$, -$SO_2N(R^aR^b)$, -$N(R^a)C(=O)R^b$, -$N(R^a)SO_2R^c$, -$N(R^a)SO_2N(R^aR^b)$, -$OC(=O)N(R^aR^b)$, or -$N(R^a)C(=O)N(R^aR^b)$,

(4) -$SO_2N(R^aR^b)$,

(5) -$N(R^a)S(=O)R^c$,

(6) -$OC(=O)N(R^aR^b)$,

(7) -$N(R^a)C(=O)N(R^aR^b)$,

(8) -$N(R^a)$-C_{1-6} alkyl-$C(=O)N(R^aR^b)$,

(9) -$N(R^a)$-$C(=O)$-C_{1-6} alkyl-$N(R^aR^b)$,

(10) -$N(R^a)C(=O)$-$C(=O)N(R^aR^b)$,

(11) -OCO_2R^c,

(12) -$N(R^a)$-$SO_2N(R^aR^b)$,

(13) -$N(R^a)$-SO_2-C_{1-6} alkyl-$N(R^aR^b)$,

(14) -$N(R^a)C(=O)R^b$,

(15) -$N(R^a)CO_2R^c$,

(16) -S-C_{1-6} alkyl-$C(=O)N(R^aR^b)$,

(17) -$N(SO_2R^c)$-C_{1-6} alkyl-$C(=O)N(R^aR^b)$,

(18) -$N(R^a)$-$C(=O)$-C_{1-6} alkyl-$C(=O)N(R^aR^b)$,

(19) -$N(R^a)$-$C(=O)$-C_{1-6} alkyl-$N(R^a)C(=O)(R^b)$,

(20) -$N(R^a)$-SO_2-C_{1-6} alkyl-$C(=O)N(R^aR^b)$,

(21) -$N(R^a)$-SO_2-C_{1-6} alkyl-$N(R^a)C(=O)(R^b)$,

(22) -$C(=O)N(R^a)$ -C_{1-6} alkyl-$C(=O)N(R^aR^b)$, or

(23) -C(=O)N(R^a)-C_{1-6} alkyl-N(R^a)C(=O)(R^b), with the proviso that the -N(Ra)- moieties are not both attached to the same carbon atom of the -C_{1-6} alkyl- moiety,

(24) -C(=O)N(R^a)-C_{1-6} alkyl-O-C_{1-3} alkyl, with the proviso that the -N(Ra)- moiety and the -O-C_{1-3} alkyl group are not both attached to the same carbon atom of the -C_{1-6} alkyl- moiety, or

(25) -C(=O)N(R^a)-C_{1-6} alkyl-$S(O)_nR^c$;

with the proviso that at least one of R^{2a} and R^{2b} is other than -H;

Q^1 is

(1) -H,

(2) -C_{1-6} alkyl, optionally substituted with from 1 to 4 substituents each of which is independently -OH, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, -CN, $-NO_2$, -N(R^aR^b), -C(=O)N(R^aR^b), -OC(=O)N(R^aR^b), -N(R^a)C(=O)N(R^aR^b), -N(R^a)-C_{1-6} alkyl-C(=O)N(R^aR^b), -N(R^a)-C(=O)-C_{1-6} alkyl-N(R^aR^b), -N(R^a)C(=O)-C(=O)N(R^aR^b), -C(=O)R^a, $-CO_2R^c$, $-OCO_2R^c$, $-S(O)_nR^c$, $-SO_2N(R^aR^b)$, -N(R^a)-$SO_2N(R^aR^b)$, -N(R^a)-SO_2-C_{1-6} alkyl-N(R^aR^b), -N(R^a)C(=O)R^b, -N(R^a)CO_2R^c, -N(R^a)SO_2R^c, or -G-C_{1-6} alkyl-C(=O)N(R^aR^b) wherein G is O or S or N(SO_2R^c),

(3) -C_{1-6} haloalkyl,

(4) -O-C_{1-6} alkyl,

(5) -O-C_{1-6} haloalkyl,

(6) halo,

(7) -CN,

(8) $-S(O)_nR^c$,

(9) $-SO_2N(R^aR^b)$,

(10) -N(R^aR^b),

(11) -C(=O)N(R^aR^b),

(12) -N(R^a)-C(=O)R^b,

(13) -N(R^a)SO_2R^c,

(14) -G-$(CH_2)_{1-2}$-C(=O)N(R^aR^b), wherein G is O, S, or N(SO_2R^c),

(15) -C(=O)-N(R^a)-$(CH_2)_{1-3}$-$[C(=O)]_{0-1}$-N(R^aR^b),

(16) -C(=O)-N(R^a)-$(CH_2)_{1-2}$H substituted with 1 or 2 -O-C_{1-6} alkyl,

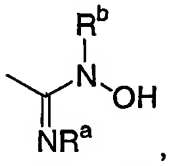
(17) -CH=CH-$(CH_2)_{0-1}$-C(=O)-N(R^a)$_2$,

(18) $-C\equiv C-CH_2OR^a$,

(19) $-C\equiv C-CH_2SR^c$,

(20) $-C\equiv C-CH_2SO_2R^c$,

(21) $-C\equiv C-CH_2N(R^aR^b)$,

(22)  ,

(23) -N(R^a)-$(CH_2)_{1-4}$-S(O)$_n$$R^c$,

(24) -N(R^a)-$(CH_2)_{1-4}$-O-C_{1-6} alkyl,

(25) -N(R^a)-$(CH_2)_{1-4}$-N(R^aR^b),

(26) -N(R^a)-$(CH_2)_{1-4}$N(R^a)-C(=O)R^b,

(27) -N(R^a)-$(CH_2)_{0-2}$-[C(=O)]$_{1-2}$N(R^aR^b),

(28) -N(R^a)-$(CH_2)_{1-4}$-CO_2R^c,

(29) -N(R^a)C(=O)N(R^a)-$(CH_2)_{1-4}$-C(=O)N(R^aR^b),

(30) -N(R^a)C(=O)-$(CH_2)_{1-4}$-N(R^aR^b),

(31) -N(R^a)-SO_2-N(R^aR^b),

(32) -R^k,

(33) -C_{1-6} alkyl substituted with one of:

(i) -R^k,

(ii) -S(O)$_n$-R^k,

(iii) -S(O)$_n$-C_{1-6} alkyl-R^k,

(iv) -C(=O)-R^k,

(v) -C(=O)-C_{1-6} alkyl-R^k,

(vi) -C(=O)N(R^a)-R^k,

(vii) -C(=O)N(R^a)-C_{1-6} alkyl-R^k,

(viii) -O-R^k,

(ix) -O-C_{1-6} alkyl-R^k,

(x) -N(R^a)-R^k,

(xi) -N(R^a)-C_{1-6} alkyl-R^k,

(xii) -N(R^a)C(=O)-R^k, or

(xiii) -N(R^a)C(=O)-C_{1-6} alkyl-R^k,

(34) -C_{2-6} alkenyl, optionally substituted with -R^k,
(35) -C_{2-5} alkynyl, optionally substituted with -R^k,
(36) -O-R^k,
(37) -C(=O)-R^k,
(38) -C(=O)-C_{1-6} alkyl-R^k,
(39) -N(R^a)-R^k,
(40) -N(R^a)C(=O)-R^k,
(41) -N(R^a)C(=O)-C_{1-6} alkyl-R^k, or
(42) -$S(O)_n$-C_{1-6} alkyl-R^k;

R^k is a carbocycle or a heterocycle;

carbocycle in R^k is independently (i) a C_3 to C_8 monocyclic, saturated or unsaturated ring, (ii) a C_7 to C_{12} bicyclic ring system, or (iii) a C_{11} to C_{16} tricyclic ring system, wherein each ring in (ii) or (iii) is independent of, bridged with, or fused to the other ring or rings and each ring is saturated or unsaturated; wherein the carbocycle is optionally substituted with from 1 to 7 substituents each of which is independently

(1) halogen,
(2) -OH,
(3) -C_{1-6} alkyl, optionally substituted with from 1 to 4 substituents each of which is independently -OH, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, -CN, -NO_2, -N(R^aR^b), -C(=O)N(R^aR^b), -C(=O)R^a, -CO_2R^c, -OCO_2R^c, -$S(O)_nR^c$, -SO_2N(R^aR^b), -N(R^a)SO_2R^c, -N(R^a)C(=O)R^b, -N(R^a)CO_2R^c, -N(R^a)SO_2R^c, phenyl, -O-phenyl, or HetX,
(4) -C_{1-6} haloalkyl,
(5) -O-C_{1-6} alkyl,
(6) -O-C_{1-6} haloalkyl,
(7) -CN,
(8) -NO_2,
(9) -N(R^aR^b),
(10) -C(=O)N(R^aR^b),
(11) -C(=O)R^a,
(12) -CO_2R^c,
(13) -OCO_2R^c,

(14) $-S(O)_nR^c$,
(15) $-N(R^a)SO_2R^c$,
(16) $-SO_2N(R^aR^b)$,
(17) $-N(R^a)C(=O)R^b$,
(18) $-N(R^a)CO_2R^c$,
(19) $-C_{3-6}$ cycloalkyl,
(20) phenyl,
(21) -O-phenyl, or
(22) HetX,

wherein each HetX is independently a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally fused with a benzene ring; and wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-O-C_{1-6}$ alkyl, $-O-C_{1-6}$ haloalkyl, oxo, or $-CO_2R^c$;

heterocycle in R^k is independently (i) a 4- to 8-membered, saturated or unsaturated monocyclic ring, (ii) a 7- to 12-membered bicyclic ring system, or (iii) an 11 to 16-membered tricyclic ring system; wherein each ring in (ii) or (iii) is independent of, brdiged with, or fused to the other ring or rings and each ring is saturated or unsaturated; the monocyclic ring, bicyclic ring system, or tricyclic ring system contains from 1 to 6 heteroatoms independently selected from N, O and S; and wherein any one or more of the nitrogen and sulfur heteroatoms is optionally oxidized, and any one or more of the nitrogen heteroatoms is optionally quaternized; wherein the heterocycle is optionally substituted with from 1 to 7 substituents each of which is independently

(1) halogen,
(2) -OH,
(3) $-C_{1-6}$ alkyl, optionally substituted with one or more substituents each of which is independently -OH, $-O-C_{1-6}$ alkyl, -CN, $-NO_2$, $-N(R^aR^b)$, $-C(=O)N(R^aR^b)$, $-C(=O)R^a$, $-CO_2R^c$, $-S(O)_nR^c$, $-N(R^a)SO_2R^c$, $-SO_2N(R^aR^b)$, $-N(R^a)C(=O)R^b$, $-N(R^a)CO_2R^c$, phenyl, -O-phenyl, HetY, or -C(=O)-HetY,

(4) -C_{1-6} haloalkyl,
(5) -O-C_{1-6} alkyl,
(6) -O-C_{1-6} haloalkyl,
(7) -CN,
(8) -NO_2,
(9) -$N(R^aR^b)$,
(10) -$C(=O)N(R^aR^b)$,
(11) -$C(=O)R^a$,
(12) -CO_2R^c,
(13) -OCO_2R^c,
(14) -$S(O)_nR^c$,
(15) -$N(R^a)SO_2R^c$,
(16) -$SO_2N(R^aR^b)$,
(17) -$N(R^a)C(=O)R^b$,
(18) -$N(R^a)CO_2R^c$,
(19) -C_{3-6} cycloalkyl,
(20) -phenyl,
(21) -O-phenyl,
(22) HetY,
(23) -$N(R^a)$-HetY, or
(24) oxo;

wherein each HetY is independently

(1) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally fused with a benzene ring; or

(2) a 5- or 6-membered saturated heterocyclic ring containing from 1 to 4 heteroatoms independently selected from N, O and S;

wherein heteroaromatic ring or the saturated heterocyclic ring is optionally substituted with from 1 to 7 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, oxo, or -CO_2R^c; and

each of Q^2 and Q^3 is independently

(1) -H,

(2) -C_{1-6} alkyl, optionally substituted with from 1 to 4 substituents each of which is independently -OH, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, -CN, -NO_2, -$N(R^aR^b)$, -$C(=O)N(R^aR^b)$, -$C(=O)R^a$, -CO_2R^c, -OCO_2R^c, -$S(O)_nR^c$, -$SO_2N(R^aR^b)$, -$N(R^a)C(=O)R^b$, -$N(R^a)CO_2R^c$, -$N(R^a)SO_2R^c$, or -$N(R^a)SO_2N(R^aR^b)$, or

(3) -C_{1-6} haloalkyl;

Z is -H or -$C(=O)N(R^aR^b)$;

each R^a is independently -H, -C_{1-6} alkyl, -C_{1-6} haloalkyl, or -C_{3-6} cycloalkyl;

each R^b is independently -H, -C_{1-6} alkyl, -C_{1-6} haloalkyl, or -C_{3-6} cycloalkyl;

each R^c is independently -C_{1-6} alkyl, -C_{1-6} haloalkyl, or -C_{3-6} cycloalkyl; and

each n is independently an integer equal to zero, 1, or 2;

or a pharmaceutically acceptable salt thereof.

15. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

16. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 14, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

17. A method of inhibiting HIV integrase in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of the compound according to claim 1, or a pharmaceutically acceptable salt thereof.

18. A method for preventing or treating infection by HIV or for preventing, treating or delaying the onset of AIDS in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of the compound according to claim 1, or a pharmaceutically acceptable salt thereof.

19. A pharmaceutical composition which comprises the product prepared by combining an effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

20. A combination useful for inhibiting HIV integrase, for treating or preventing infection by HIV, or for preventing, treating or delaying the onset of AIDS, which is a therapeutically effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of an HIV infection/AIDS antiviral agent selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors and nucleoside HIV reverse transcriptase inhibitors.